A STUDY ON SERUM LEVEL OF FIBRINOGEN AND ITS PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH ACUTE ISCHEMIC STROKE IN KILPAUK MEDICAL COLLEGE HOSPITAL

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for the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE

CHENNAI

April - 2014

BONAFIDE CERTIFICATE

This is to certify that the Thesis-**"A Study on serum level of fibrinogen and its prognostic significance in patients with acute ischemic stroke in kilpauk medical college hospital"** is a genuine work done by Dr.A.T.APPURAJ, Post-graduate student in Department of Medicine, Government medical college, Kilpauk,under the guidance of Prof. Dr.N. GUNASEKARAN, M.D., DTCD, Head of the Department of Medicine, Kilpauk Medical College.

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DECLARATION

I, **Dr. A.T.APPURAJ**, solemnly declare that the dissertation titled **"A Study on serum level of fibrinogen and its prognostic significance in patients with acute ischemic stroke in kilpauk medical college hospital"** has been prepared by me. This is submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of MD degree Branch I (General Medicine).

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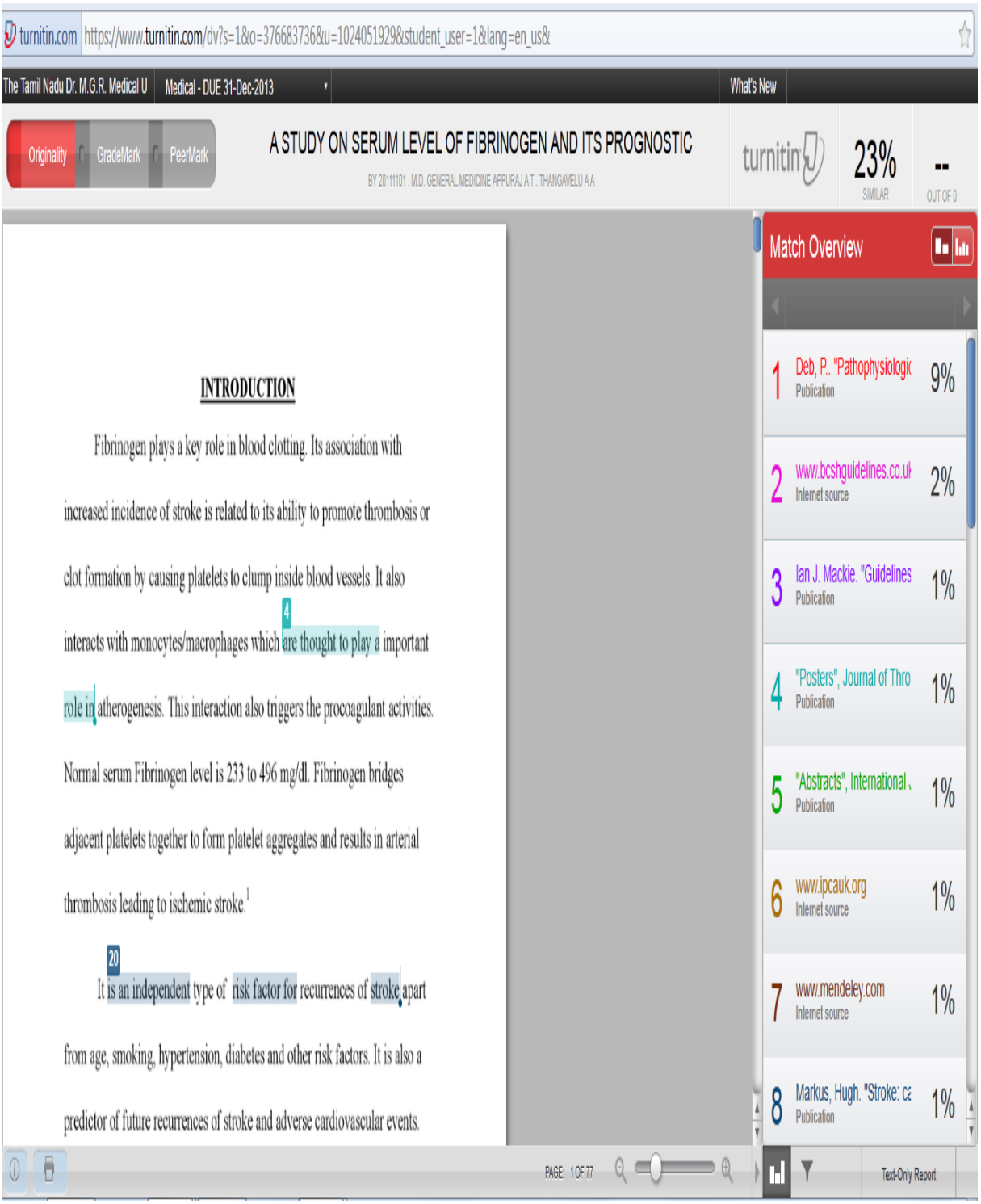
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INTRODUCTION
Fibrinogen plays a key role in blood clotting. Its association with increased incidence of stroke is related to its ability to promote thrombosis or clot formation by causing platelets to clump inside blood vessels. It also interacts with monocytes/macrophages which are thought to play a important role in atherogenesis. This interaction also triggers the procoagulant activities. Normal serum Fibrinogen level is 233 to 496 mg/dl. Fibrinogen bridges adjacent platelets together to form platelet aggregates and results in arterial thrombosis leading to ischemic stroke.[1]
It is an independent type of risk factor for recurrences of stroke apart from age, smoking, hypertension, diabetes and other risk factors. It is also a predictor of future recurrences of stroke and adverse cardiovascular events.
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ABSTRACT

BACKGROUND AND OBJECTIVES:

Stroke is the third commonest cause of death worldwide, after coronary heart disease (CHD) and all types of cancer. Fibrinogen is an independent risk factor for stroke and also predictor of future recurrences of stroke. Hence, Measurement of fibrinogen levels could be more useful than others as it is more specific to vascular disease. The objective of this study is to test the hypothesis that increased fibrinogen in ischemic stroke is related with severe onset and poor prognosis.

METHODS:

Patients admitted with history of acute onset of stroke in Department of Medicine within 48 hours of onset of stroke were enrolled in after excluding the exclusion criteria. Age and sex matched persons not having focal neurologic deficit and after verifying exclusion criteria were taken as controls. The study was done in 100 subjects ,50 cases and 50 controls. Fibrinogen was measured quantitatively by Clauss method. Severity was assessed using National Institute of Health Sciences Stroke Scale at admission. Reassessment of morbidity and mortality using Modified Rankin's scale scores at one month follow-up.

RESULTS:

The mean fibrinogen level among cases was 612.20 and controls was 296.80, with a p value of 0.001 (< 0.05. In the study, the mean fibrinogen levels are higher in cases than controls irrespective of presence or absence of other risk factors,which was statistically significant($p<0.05$). It was clear from the study that the acute ischemic stroke was very severe in patients with higher fibrinogen levels. Also, the outcome at the end of one month was poor in patients with higher fibrinogen levels during stroke onset.

KEY WORDS: Fibrinogen, Acute Ischemic stroke.

INTRODUCTION

Fibrinogen plays a key role in blood clotting. Its association with increased incidence of stroke is related to its ability to promote thrombosis or clot formation by causing platelets to clump inside blood vessels. It also interacts with monocytes/macrophages which are thought to play a important role in atherogenesis. This interaction also triggers the procoagulant activities. Normal serum Fibrinogen level is 233 to 496 mg/dl. Fibrinogen bridges adjacent platelets together to form platelet aggregates and results in arterial thrombosis leading to ischemic stroke.[1]

It is an independent type of risk factor for recurrences of stroke apart from age, smoking, hypertension, diabetes and other risk factors. It is also a predictor of future recurrences of stroke and adverse cardiovascular events. Hence, fibrinogen levels are to be measured in patients with stroke at the earliest and to be treated.[1]

Fibrinogen plays significant role in a number of physiological and pathological processes like inflammation and atherogenesis and thrombogenesis. This is due to infiltration of blood vessel wall by fibrinogen, increase in blood viscosity and its, haemorrheological effects, increased aggregation of platelets and subsequent thrombus formation. The binding of fibrinogen to ICAM-1 receptors on vascular endothelium mediate the platelet adhesion. Fibrinogen causes damage of endothelium and its dysfunction by a

variety of mechanisms. This is supported by the decrease in intimal fibrinolytic activity and plasminogen level observed in cardiovascular disease. Fibrinogen plays a role in the process of aggregation of platelets. It crosslinks the platelets by the process of binding the glycoprotein IIb-IIIa receptor on the surface of platelets. This is more relevant with the adventure of glycoprotein IIb-IIIa receptor inhibitors. Hence, Measurement of plasma fibrinogen levels could be more useful than other acute phase reactants such as C-reactive protein, as fibrinogen is more specific to vascular disease. The primary objective of this study dissertation is to test the hypothesis that increased fibrinogen in ischemic stroke is related with poor prognosis. Besides, the dissertation also identifies the association of fibrinogen with other multiple variables like age, sex, body weight, smoking, cholesterol, hypertension and diabetes.[2]

REVIEW OF LITERATURE

FIBRINOGEN:

STRUCTURE OF FIBRINOGEN:

Fibrinogen is a glycoprotein soluble in nature, synthesised predominantly in liver and secreted into plasma. It is about 45 nm long and 9 nm in diameter with a molecular mass of about 340 kilo Dalton.

Fibrinogen molecule is a large tri-nodular glycoprotein with two symmetrical half molecules. One half contains three polypeptide chains (A α, B β, gamma) linked to by disulphide bonds. The NH-2 terminal of all six polypeptide chains form NH-2 terminal disulphide knot, which lies in the central nodule or E- domain which is 5 nm in diameter. The c-terminal two thirds of both B β and gamma chains lie in the outer two D- domain nodules. Between E- and D- domains ,a stretch of about 120 amino acids from each of the three chains form an 'coiled coil domain' ,which is an α helical structure. This region is supported by disulphide rings on both sides. This disulphide rings make fibrin mechanically strong and resistant to proteolysis.[3]

The A α polypeptide chain is divided into three distinct domains and contain 610 amino acids. The first section of A α chain (residue 1- 194) contains a region (residues 45-161) which by disulphide bonds is linked to B β and

gamma chains. It also forms part of α helix or coiled coil domain. It also contain fibrinopeptide A and the polymerisation site in the E domain.

The middle section of A α chain (240 – 424 residue) is rich in apolar aminoacids. It contains ten tandem repeats each of thirteen aminoacids long. The bridging regions of first two sections contain a protease sensitive domain having high content of pralines and several plasmin cleavage sites. There are two glutamine residues in middle section of A α chain which serve as cross linking receptor sites for factor XIII a.

The third section is the hydrophilic C- terminal of the molecule (residue 425- 610). It contain the cross linking sites for fibronectin and α -2 anti plasmin. There are two (arginine,glycine, aspartic acid) sequences in A α chain that play a role in cellular adhesion events.[3]

The B β polypeptide chain contains 461 aminoacids which is also divided into three sections. The first 80 residues form first section which contains fibrinopeptide B sequence (residue 1-15) and a site that support endothelial cell spreading and proliferation (residue 16 – 42). The middle section (residues 81 – 192) forms part of coiled coil domain and is linked by disulphide bonds to A α and gamma chains. The C terminus forms one of the independently folded subdomain of D domain.

The gamma chain is 411 aminoacid long and is divided into three section. The first 18 aminoacids form part of NH-2 terminal disulphide knot. The middle section contain aminoacids 19- 135 and contain disulphide rings which link this region to the A α and Bβ chains in the coiled coil domain. The C terminal section contain aminoacids 136 – 411 and form globular subdomain of the D domain. In this region, there is D domain polymerisation site, factor XIII a cross linking site and binding domain for platelet aggregation.

In human, the plasma fibrinogen has two distinct forms of gamma chain. The gamma[1] chains constitute 15% and contain an extended C- terminal. It is produced by alternative polyadenylation of the last intron of gamma chain gene.

The B β and gamma chains contain asparagine residue which serve as N-glycosidic linkage for carbohydrate attachment. In diseases with hepatic injury, a fetal form of fibrinogen is produced which has more sialic acid attached to carbohydrate side chain. It results in defective polymerisation of fibrins and also associated with cirrhosis and hepatomas. This defective polymerisation in fetal fibrinogen does not cause bleeding but can produce significant prolongation of clotting time in in-vitro assays.[3]

SYNTHESIS OF FIBRINOGEN:

Fibrinogen is exclusively synthesised in liver by hepatocytes. Three genes located separately on chromosome-4 (Ch4q23-q32) under coordinated

control synthesize the three chains. This is followed by subsequent assembly of these chains and carbohydrate side chain attachment, after which the mature molecule is secreted into circulation. The half life is 72- 108 hrs (average 100 hr) and the catabolic rate is 25% per day. The fibrinogen turnover rate is 1.7 to 5 gram per day or 30 – 60 mg per kilogram per day.[4]

FUNCTIONS OF FIBRINOGEN:

Fibrinogen plays an important role in three major processes which are as follows:

1) During blood coagulation process, soluble fibrinogen is converted into insoluble fibrin.
2) The polymerised fibrin acts as a template and activates fibrinolytic system, which modulates fibrin deposition and clot dissolution.
3) Fibrinogen binds to Gp IIb/IIIa receptor on platelets and cause platelet aggregation and also to endothelial cells where it participate in tissue repair.

There are three distinct phases in conversion of fibrinogen to fibrin which is insoluble. They are:

a) Thrombin mediated enzymatic cleavage of fibrinopeptide.

b) Polymerization of fibrin.

c) Stabilisation of fibrin through covalent cross linking which is mediated by factor XIIIa.

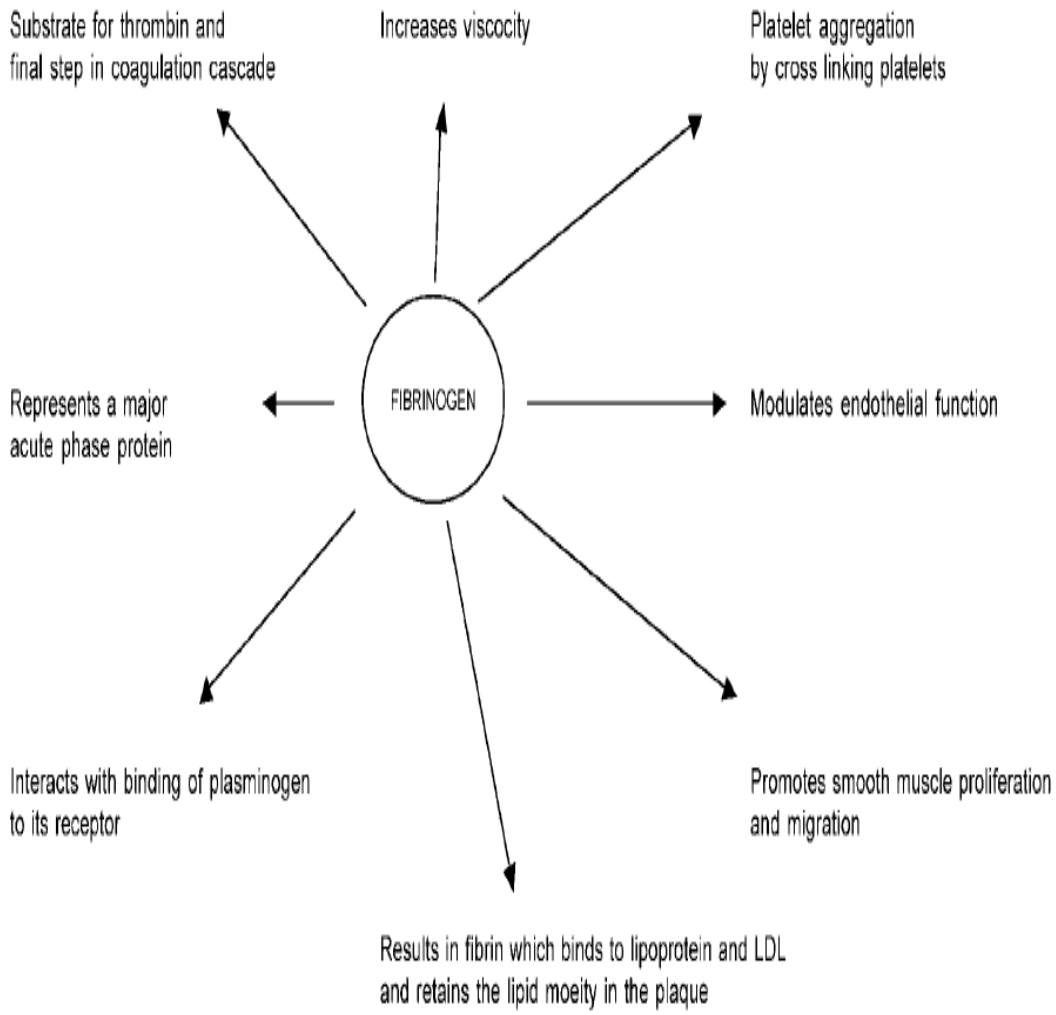


Figure 1. Plasma fibrinogen, thrombogenesis and atherogenesis.

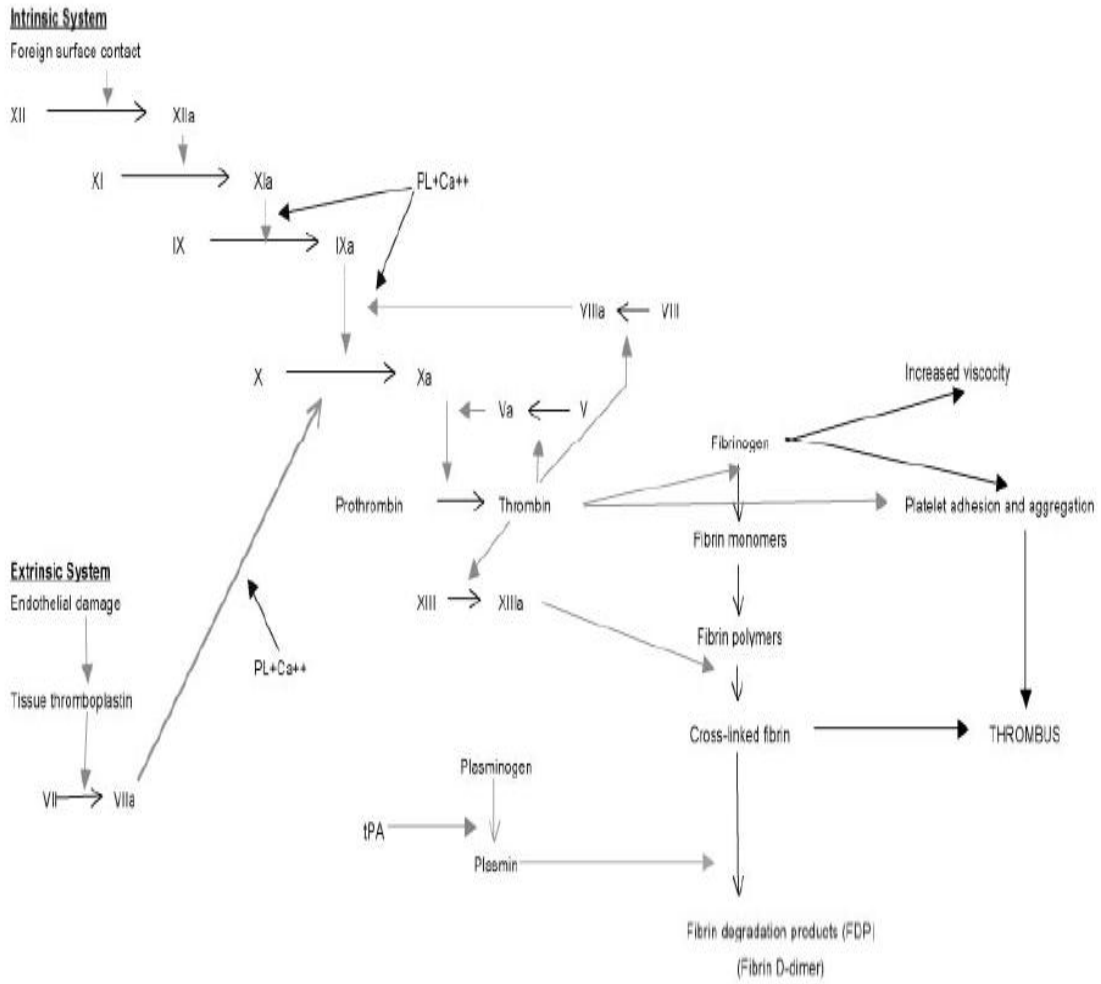


Figure 2. Interaction(s) between the coagulation system and fibrinolytic system. PL, phospholipid.

In the first phase, there will be cleavage of A α chain and of B β chain by thrombin leading to release of two molecules of fibrinopeptide A and two fibrinopeptide B per molecule of fibrinogen.This results in fibrin monomer formation. The constituent chains of fibrin monomer are now termed as α-, β- and gamma-chain.[3,4]

The next phase involves reciprocal non covalent interaction of molecular determinants in the E region of the molecule which are exposed after removal of

FPA, with complementary binding site located in D region of an adjacent fibrin monomer. This results in dimer that is arranged in a half-staggered overlap. The dimer continues to grow in length by addition of fibrin monomers. The result of which is formation of a two stranded half-staggered polymer termed as protofibril. The protofibril is the basic structural unit of fibrin clot.

The two D domains of longitudinally aligned fibrin molecules in each row of protofibril come into close contact with one another by the process of half staggered polymerization.This results in further stabilisation of non-covalently associated fibrin protofibril. The process of polymerisation continues with formation of long double stranded protofibrils that ultimately associate laterally to form thick fibrin bundles.

The FPB cleavage occur during initial phase of polymerisation and expose the determinant which are complementary with binding sites located in C- terminal of α chain. This step increases the rate of formation of thin fibrils and the lateral aggregation to form thick fibrin fibers.

The formation of covalent amide bonds between the ϵ- amino group of specific lysine residues and gamma- CONH2 groups of certain glutamine residues through factor XIIIa mediation is characteristic of final stage of fibrin formation.

The dimerization of gamma chain is then followed by progressive covalent linking of multiple α chains. The net result of covalent stabilisation is that the clot becomes more compact and resistant to mechanical disruption and dissolution by plasmin.[3,4]

FIBRINOGEN MEASUREMENT:

There are variety of tests for fibrinogen that can been used by laboratories. Some tests are used for emergency situations where an estimate of whether normal or grossly decreased levels can be made out.[5]

TYPES OF FIBRINOGEN ASSAY:

THE CLAUSS ASSAY (CLOTTING RATE ASSAY):

In this type of assays, thrombin (from 35 to 200 U/ml) is added to dilute the plasma and the clotting time is measured. The result is compared with a curve, prepared by clotting a series of dilutions of a reference plasma sample, the fibrinogen concentration of which is known and the result in g/l is obtained. This technique is relatively time consuming. The end-point depends on tensile strength of the clot and this makes them sensitive at low fibrinogen levels. They are affected by heparin therapy.

Photo-optical systems depend on change in optical density resulting due to fibrin formation.[5,6]

PROTHROMBIN TIME DERIVED TESTS(PT-Fg):

The estimation of Fibrinogen derived from the prothrombin time (PT-Fg) have been widely used in recent years. The analyser is calibrated by performing prothrombin time on a plasma (or series of dilutions of plasma) with known fibrinogen concentration and then by plotting a graph of optical change against the fibrinogen concentration. The resulting optical change in each test sample is then converted to a fibrinogen value.[5,6]

CLOTTABLE PROTEIN ASSAY:

These type of assays are very accurate and have been used as reference assays for fibrinogen. In this assay, Thrombin is added to plasma in the absence of calcium ions and the clot is washed. It is then dissolved in alkaline urea or other reagents, followed by spectrophotometric protein assay or estimation.[5,6]

IMMUNOLOGICAL ASSAY:

There are number of immunological assays are available namely, enzyme linked immunosorbent assays (ELISAs), radial immunodiffusion and electrophoretic techniques.[5,6]

FIBRINOGEN TITRE:

It is an emergency test where plasma is diluted in different types of buffer before the addition of thrombin. The resultant titre is reported as the last dilution

to display a clot after a given incubation time. This test can be performed inspite of the presence of various inhibitors The results are inaccurate and it is time consuming and also does not lend itself to automation.[5,6]

GRAVIMETRIC ASSAYS:

In this assays, fibrinogen is clotted from the dilute plasma by using a strong thrombin solution and calcium chloride. The clot thus formed is compressed to express solution and non-clotted proteins which is then washed in saline, and dried and weighed on an accurate microbalance.

SULPHITE PRECIPITATION TECHNIQUES:

This techniques have been described by Rampling & Gaffney in 1976 but are unreliable in some clinical situations (like in patients with acute phase reaction). They are not normally used in hospital haematology laboratories.[5,6]

PRE-TEST VARIABLES:

The WHO recommended anticoagulant for fibrinogen assay is tri-sodium citrate in a strength of 0.105–0.109 mol/l, (1 part anticoagulant: 9 parts blood), such as used for other blood coagulation tests. The inadequate filling of the collection tube affects this ratio which leads to inaccurate results. For haematocrit values greater than 0.55 l/l, the final blood citrate concentration requires an adjustment and there are charts available which indicate the amounts

of anticoagulant and blood that are to be mixed. Samples with any clots or marked haemolysis should be rejected.[7]

REGIONAL VARIATIONS IN PLASMA FIBRINOGEN LEVELS:

Several studies showed that that the normal plasma fibrinogen level ranges from 2.3 to 4.0 gram / dl. This is strongly influenced by method of measurement. The regional variations found in fibrinogen levels are as a result of undefined environmental factors and are not related to patient characteristics.[7,8]

FIBRINOGEN ABNORMALITIES:

The fibrinogen abnormalities can be either congenital or acquired. In both cases there may be a qualitative or quantitative abnormality in fibrinogen. In certain cases both abnormalities can be present in the same patient.

a) CONGENITAL DISORDERS:

i) CONGENITAL AFIBRINOGENEMIA:

It is inherited as autosomal recessive disorder with both parents acting as carriers. Usually the fibrinogen level is less than 0.1 gram per litre of plasma. It manifests as umbilical cord bleeding, cutaneous bleeding, gastrointestinal haemorrhage, intracranial bleed (rarely) and intra-articular bleed. The laboratory evaluation shows prolongation of PT, a PTT and thrombin time

with zero or trace plasma fibrinogen levels. It can be treated by transfusion of cryoprecipitate or fibrinogen concentrates and anti fibrinolytic agents.[6,7]

ii) CONGENITAL HYPOFIBRINOGENEMIA:

It is inherited as an autosomal dominant or autosomal recessive disorder. The plasma fibrinogen level is between 0.1 gram per litre and lower limit of normal reference range for that laboratory. The clinical manifestations include umbilical cord bleeding, cutaneous bleeding, gastrointestinal haemorrhage, intracranial bleed (rarely) and intra-articular bleed. The investigations will show normal aPTT, prolonged PT and mildly prolonged TT. They are treated with cryoprecipitate or fibrinogen concentrates and anti fibrinolytic agents.[6,7]

iii) CONGENITAL DYSFIBRINOGENEMIA:

It is inherited as autosomal dominant or recessive disorder. This is characterised by synthesis of abnormal fibrinogen molecule which exhibits altered functional properties and altered thrombin mediated conversion to fibrin. It usually manifests as thrombosis and there will be no evidence of hemorrhage. The investigations will show normal aPTT and PT. There will be increased thrombin time and reltiplase time. The fibrin assay is normal. There will be

higher fibrinogen for immunogenic than thrombin clotting method. They are treated with cryoprecipitate or fibrinogen concentrates with anticoagulants for thrombosis.[6,7,8]

b) **ACQUIRED DISORDERS[7,8]**:

i)HYPOFIBRINOGENEMIA:

It occurs as a result of one of the following causes:

a) Decreased biosynthesis of fibrinogen by hepatocyte due to decompensated liver disease and fulminant hepatic failure.
b) Disseminated intravascular coagulation due to increased consumption.
c) Drugs like valproic acid and L-Asparaginase
d) Alcohol consumption- it decreases fibrinogen level by 0.78% for each 10 gram of alcohol consumed.
e) Fibrinolytic therapy will reduce fibrinogen level for one or two days.

ii) DYSFIBRINOGENEMIA:

It can be due to:

a) Idiopathic.
b) Liver disease- 50% of patients with cirrhosis, hepatitis and hepatomas show functional abnormality in fibrin polymerization.
c) Multiple myeloma - Abnormal fibrin monomer polymerization.

d) Paraneoplastic syndrome in association with hypernephroma.

e) Autoimmunity – antibody mediated functional abnormality in SLE, Ulcerative colitis and post- necrotic cirrhosis.

iii)HYPERFIBRINOGENEMIA:

1) **Age** :

As age advances there will be increase in fibrinogen level.[9,10]

2) **Sex** :

It is more in males compared to females.[9]

3) **Race** :

Fibrinogen levels are more in blacks than whites.[9]

4) **Smoking** :

It is has a positive correlation with plasma fibrinogen level.[9]

The high fibrinogen level in heavy smokers is usually due to:

- Endothelial injury by leading to activation of coagulation system.[11]
- Release of interleukin-6 by lung macrophages which increase the hepatocyte fibrinogen synthesis.[12]

5) **Physical activity**:

The fibrinogen concentration is inversely proportional to physical activity.[12,13]

6) **Diet** :

Increased carbohydrate and fat, decreased ω-3 and ω-6 PUFA's and fibre increase fibrinogen level.

7) **Obesity** :

Obesity results in increased viscosity and fibrinogen levels.

8) **Hyperlipidemia** :

High cholesterol, LDL, Lp(a) and elevated triglycerides are associated with high fibrinogen levels which in turn consistent with increased thrombotic complications in dyslipidemias.

9) **Hypertension** :

Fibrinogen levels are more in hypertensives than normotensive persons.

10)**Diabetes mellitus**:

There is positive correlation between serum fibrinogen, hyperglycemia and increased glycated haemoglobin. Hence it will be more in diabetics than non – diabetic individuals.

11) **Ischemic heart disease**:

There is a positive correlation with fibrinogen level and severity of coronary artery disease.

12) **Left ventricular dysfunction**:

The increased fibrinogen level seen in left ventricular dysfunction is responsible for intra cardiac thrombus and systemic thromboembolism.[14]

13) **Atrial fibrillation**: increased in chronic atrial fibrillation.

14) **Psychological and mental stress** increases fibrinogen level.

15) **Cerebrovascular disease**:

Increased fibrinogen level is associated with stroke, TIA incidence and carotid atherosclerotic progression and peripheral vascular disease.

16) **Social class**:

Fibrinogen levels are higher in low socioeconomic class individuals.

17) **Family history of IHD**.

18) **Dental disease**: Chronic inflammatory gingival and periodontal infections.

19) **Elevated leukocyte counts**:

20) **Acute inflammation and infections**:

As an acute phase reactant fibrinogen is elevated by three fold in acute inflammation and infections.

21) **Genetics**:

The plasma fibrinogen formation is significantly influenced by genetics. Variation occurring in β fibrinogen locus affects fibrinogen concentration. The β gene controls the formation of Bβ chain, the rate limiting step in synthesis of fibrinogen.[15]

STROKE

DEFINITION:

Stroke is defined by WHO as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of vascular origin'. This includes both cerebral infarction or intracerebral and subarachnoid hemorrhage. A time window of 24 h distinguishes stroke from transient ischaemic attack (TIA), which is defined as a neurological deficit lasting less than 24 h. The term cerebrovascular disease compasses all vascular disease affecting the brain including stroke, vascular dementia, and asymptomatic cerebrovascular disease.[16]

HISTORY:

Hippocrates (460-370 BC), first described stroke like symptoms as 'the signs of impending apoplexy are attacks of numbness and anaesthesia'. Galen (131-201 A) first described the anatomy of brain and its blood supply by animal dissection. Johan Jacob Wepfer (1629-1695) first described that occlusion of carotid and vertebral arteries are the cause of apoplexy and also bleeding inside brain as an important cause of stroke. Thomas Willis described the circular anastamosis of blood vessels at the base of brain and recognised transient ischemic attacks and embolic phenomenon.[16,17]

EPIDEMIOLOGY:

Stroke is the third commonest cause of death worldwide, after coronary heart disease (CHD) and all types of cancer. Unlike the Caucasians, Asians have a higher prevalence of stroke. The number of persons who died from stroke was more than three times that for CHD, among the Asians.[17] In one of the reports, the stroke mortality rate was 44 to 102.6/100,000 for males in Asia, when compared to 19.3 for white males in Australia.

In 1980s, the prevalence rate of stroke were around 500-700 per 100,000 in western countries and 900 per 100,000 in Asia.[18] The first community-based study on stroke in India was done in Vellore in South India during 1969-71, and then a study in Rohtak during 1971-74.[19] It was estimated that stroke represented 1.2 % of the total deaths in the country including all ages. The stroke death proportion increased with age and in > 70 years of age stroke contributed to 2.4% of all deaths. The gender ratio of death due to stroke was 1.[20]

PATHOPHYSIOLOGICAL CLASSIFICATION OF STROKE:

ISCHAEMIC STROKE

Large artery

Cardioembolic

Lacunar (small vessel disease)

Other determined aetiology

Undetermined aetiology

Multiple possible aetiologies[21,22]

CEREBRAL HAEMORRHAGE

Primary subarachnoid haemorrhage

Primary intracerebral haemorrhage

DEFINITIONS:

Large artery stroke:

Occlusion or stenosis (>50%) in the large extracranial or intracranial cerebral arteries (carotid, vertebral, basilar, anterior cerebral, middle cerebral, posterior cerebral) with ischaemia in that arterial territory.

Cardioembolic stroke:

One or more of the following conditions:

Mechanical prosthetic heart valve, atrial fibrillation, myocardial infarction within last 2 months, dilated cardiomyopathy/congestive heart failure at stroke onset, endocarditis, sick sinus syndrome, atrial myxoma, left ventricular thrombus.

Lacunar stroke:

Lacunar syndrome (pure motor stroke, pure sensory stroke, ataxic hemiparesis, clumsy hand dysarthria) characterised by either no lesion on brain imaging or a deep infarct (≤ 1.5 cm diameter) in the location consistent with the clinical syndrome.[21,22]

STROKE RISK FACTORS:

A number of well recognised conventional risk factors for stroke are known already. They include both modifiable and non- modifiable factors.

Age:

It is one of the strongest risk factor for both cerebral infarction and haemorrhage. The incidence of stroke doubles with each successive decade above the age of 55 years (Wolfe 2000).

Gender:

Regarding gender, being a male is a risk factor for stroke. Overall, women will suffer stroke during their lifetime due to their greater life expectancy.

Hypertension:

Increase in blood pressure is a major risk factor for stroke. It has a strong and independent association with both ischemic and haemorrhagic stroke (Collins and Mac Mahon 1994). The stroke risk almost doubles with each 7.5 mmHg increase in diastolic blood pressure.[23]

Smoking:

Studies showed that cigarette smoking is an important risk factor of stroke. The relative risk is approximately 2.

Diabetes mellitus:

The relative risk of stroke in association with diabetes is approximately 2–2.5. It is also a risk factor for atherosclerosis in casrotid arteries.

Cholesterol:

An Increase in total cholesterol and low-density lipoprotein cholesterol are strong risk factors for ischaemic heart disease while increased level of high-density lipoprotein cholesterol seems to be protective. This relationship appears to be weak in case of stroke. Recent trials showed that, cholesterol reduction with statin therapy, reduces risk of stroke (Byington et al. 2001, Heart Protection Study Collaborative Group 2002). Also statins do have additional therapeutic effects such as reduce stroke incidence through atherosclerotic plaque stabilization and upregulation of endothelial nitric oxide synthase.

Body mass index:

It is an independent risk factor for stroke in both smokers and non-smokers. A secondary increase in inflammation due to increased levels of cytokines in adipose tissue could be a mechanism through which obesity increases stroke risk.

Physical exercise:

Decreased physical activity is associated with an increased risk of stroke. Increase in physical exercise acts through reducing blood pressure.[23]

Plasma fibrinogen:

The association between increased plasma fibrinogen and stroke is strong and consistent. This relationship is partly confounded by smoking as it increases stroke risk through increased fibrinogen.[24]

Alcohol:

Alcohol consumption in large volumes is a risk factor for stroke. This may due to increase in blood pressure and also due to atrial fibrillation or myocardial damage secondary to cardiomyopathy.

Ethnicity:

Among different ethnic groups, there is marked difference in incidence of stroke and the distribution of subtypes of the stroke. The incidence of stroke is increased in Black Americans and United Kingdom African Caribbeans compared with Caucasians (Gillum et al. 1999). Stroke incidence also appears to be higher in Chinese (Thorvaldsen et al. 1995), and intracranial atherosclerosis appears to be more common.[25]

Homocysteine:

Homocysteinuria is associated with very high levels of serum homocysteine is associated with an increased risk of stroke at an early age. This is due to endothelial dysfunction and accelerated atherogenesis or increased thrombosis.[26]

Socio-economic conditions:

This is likely to act through a number of factor such as smoking, poor diet and lack of exercise which are all associated with low socio-economic status.

Recent infection and inflammation:

Majority of case control studies on ischaemic stroke showed an association between recent infection and stroke, which are determined by history of recent respiratory tract or other symptoms and by serological testing (Grau *et al*.1995). It occurs as a result of inflammatory changes which lead to a prothrombotic state and acute endothelial dysfunction.[27]

Diet:

Increased salt intake is associated with increased blood pressure. It is estimated that a 100 mmol increase in sodium intake will increase blood pressure by 10 mmHg which leads to about a 34 per cent increased risk of stroke (Law 1996). Higher vitamin C levels (high fruit and vegetable intake) are associated with a lower stroke risk which acts through an anti-oxidant effect. Folate may also reduce the stroke risk by reducing homocysteine concentration (Homocysteine Lowering Trialists' Collaboration 1998).

Oral contraceptives:

Studies showed a increased stroke risk associated with the oral contraceptive pill which is definite.[28]

Migraine:

Stroke may complicate a migraine attack. Migraine itself appears to be a risk factor for stroke in young women. Studies have showed a positive association between migraine and stroke.[29]

CardioVascular disease:

Atrial fibrillation of both Rheumatic and non- Rheumatic origin are important risk factors for stroke.[30]

Transient ischemic attacks:

It is also an one of the risk factors for stroke. One out of every six patients would be affected by thrombotic stroke after two to four years.

Polycythemia:

It causes stroke due to hyperviscosity and sluggish blood flow.

Prior stroke:

The annual incidence of recurrent stroke is 142 per one lakh for the first stroke and 52 for subsequent stroke as observed by the national stroke survey.[30]

PATHOPHYSIOLOGY OF ISCHEMIC STROKE:

Ischemic stroke can manifest as thrombotic stroke, embolic stroke, systemic hypoperfusion or venous thrombosis. Compromised blood perfusion is the basic pathology in (85–90%) of strokes. The brain tissue is vulnerable ischemia because of low respiratory reserve and dependence on aerobic

metabolism. Therefore, core region undergoes immediate death, while penumbra region may be partially injured which has a potential to recover.

CELLULAR LEVEL EFFECTS:

Ischemia induced brain damage is by activation of the ischemic Cascade. This lead to local depletion of oxygen or glucose which leads to failure of production of ATP. This affect factors necessary for cell survival which are dependant on energy. This leads to a series of events resulting in cell injury and death. The extent of damage depends on duration, severity, and its location.

The mechanisms involved in tissue injury/neuro protection are:

• Depletion of cellular energy store due to failure of mitochondria.

• Deleterious effects due to functional loss of membrane ion pumps.[31]

• Release of excitatory neurotransmitters:

Glutamate:

There is release of excitatory neurotransmitters due to ischemic cascade, like glutamate and aspartate. The neuronal plasticity is maintained by glutamate which plays a vital role in it. But there will be an uncontrolled release of these transmitters in ischemic areas which mediate an excitotoxic synaptic transmission.The release of excitatory neurotransmitter, glutamate occur through six known mechanisms[32,33]:

(i) Reversal of uptake by transporters on plasma membrane,[34]

(ii) Cell swelling which results in anion channel opening ,

(iii) Calcium dependent exocytosis,

(iv) The cystine–glutamate antiporter mediated glutamate exchange,[35]

(v) Ionotropic purinergic receptors mediated release.

(vi) Unpaired connexons, 'hemichannels' which are functional, on the cell surface.[36]

Synaptosomal-associated protein 25 (SNAP-25)[37]:

It is localised in nerve endings and axons. It is a neuron-specific protein and is involved in synaptic vesicle exocytosis,axonal outgrowth and release of transmitter.

Studies showed that SNAP-25 is differentially regulated in ischemic stroke. Marti et al. demonstrated that there is increase in SNAP-25 mRNA levels in the infarct and penumbra region of stroke patients and it occurs mainly during the first 6 days after stroke. Astrocytes contain proteins that are essential for glutamate sequestration into vesicles. Those proteins are[38]:

i) Vacuolar type H+-ATPase (V-ATPase)

ii) Vesicular glutamate transporters (VGLUT) 1, 2 and 3.[39]

• Production of Reactive oxygen species and Oxygen free radicals[40]:

These damage endothelium by reacting with them. It also initiates the apoptotic pathway.

• Apoptosis:

It is known that necrosis occurs in ischemic core, likewise apoptosis occurs in the peripheral neurons.This results in an early gene expression of p53 and Bcl-2[42] and release of pro-apoptotic molecules.[41]

• Neuroprotection[49]:

The ischemic cascade activates a variety of neuroprotective mechanisms which protect against cell death due to apoptosis and necrosis. These include:

◦ Heat shock protein 70 (HSP70).[43]

◦ Bcl-2 gene family.[44]

◦ Prion protein (PrPc).[45]

◦ Neurotrophin-3 (NT-3).[46]

◦ Interleukin-10.[47]

◦ Granulocyte-colony stimulating factor (G-CSF).[48]

ISCHEMIC PENUMBRA:

The ischemic cerebrovascular tissue has 2 layers:

(a) Inner zone with severe ischemia having blood supply < 10–25%, which shows necrosis of neurons and glial elements.

(b) Outer zone with less severe ischemia (penumbra) that is supplied by collaterals. This zone contain cells that can be saved by timely therapeutic intervention.[50]

Immediately following an ischemic event, the centre core is perfused at 10–12 ml/100 g/min or less and the ischemic area around it is hypoperfused at less than 18–20 ml/100 g/min. It is at risk of dying within hours. The penumbra is perfused at 60 ml/100 g/min and is less likely to die. Neurons in the penumbra are dysfunctional and may recover if reperfused in time. That is why the current protocols favour early pharmacologic intervention for re-canalization.[51]

CEREBRAL EDEMA:

It accounts for much of the death and disability and hence of much concern. This attributes to the effect of neurogenic inflammation mediated through neuropeptides like substance P.

Klatzo classified edema as:

• Cytotoxic edema:

This type of edema evolves within hours and is reversible. There will be swelling of the cellular elements of the brain like neurons, glia, and endothelial cells due to failure of ATP dependent ion transport and due to release of oxygen-derived free radicals.

• Vasogenic edema:

This type of edema occurs over hours and days. It is irreversible. It causes increased permeability to serum proteins. This results in increased extracellular fluid volume and increased intracranial pressure (ICP). This causes

compartment shift within the brain and hence compresses neural structures and cerebral arteries. A sustained rise in intracranial pressure results in persistent ischemia and irreversible damage to brain cells.When severe may lead to cerebral herniation and potentially death.[52,53]

EFFECTS ON STRUCTURAL INTEGRITY OF BRAIN:

Hypoxia causes loss of structural integrity of brain and blood vessels mediated the release of matrix metalloproteases(MMP).[58] The results in breakdown of the blood–brain barrier, which manifests as cerebral edema.[54,55]

- Angiogenesis[56]:

  This occurs through:

  (a) Inhibition of hypoxia-inducible factor-1 (HIF-1) degradation which inturn stimulates VEGF that is important for angiogenesis.

  (b) Inflammation-associated infiltrates mediated by secretion of angiogenic growth factor.

- Activation of the immune mechanism by ischemia.[57]

ATHEROSCLEROSIS AND STROKE:

The onset of atherosclerotic changes to precipitation of acute ischemic stroke is complex.

The changes include[59]:

(a) Fatty streak.

(b) Massive extracellular lipid at the branching points of vessels.

(c) Complicated fibrous plaques.

EVENTS IN ATHEROGENESIS:

(A) Injury to arterial wall[59]:

Ross had hypothesized that, atherosclerosis occurs due to effect of complex interplay among monocytes, lipoproteins, platelets, lymphocytes, and smooth muscle cells in the vascular intimal layer.

(B) Foam cell transformation by monocytes and T- Lymphocytes.[60]

(C) Oxidation of LDL-cholesterol**.**

(D) Smooth muscle cell migration and its proliferation.[61]

(E) Platelet aggregation and adhesion along with denudation of epithelium.[62]

(F) Fissuring of plaque and formation of thrombus.[63,64]

• Subtypes of ischemic stroke due to thrombosis:

◦ **Atherothrombotic occlusion**:

This is the most common cause of primary large vessel occlusive cerebrovascular disease and also stroke.

◦ **Embolism:**

They may due to cerebral arterial atherothrombosis and also may arise from other cardiac sources and deep vein thrombosis.

◦ **Microatheroma:**

They are due to influx of fat like materials resulting in lipohyalinosis. It usually affect small vessels and causes lacunar strokes.[65]

(*G*) Plaque fissuring and its outcomes like partial or complete occlusion due to thrombus.

(*H*) Cerebral atherothrombosis and its evolution:

Thrombosis usually evolves over few minutes, or even take hours or days.

A stroke that progresses due to increasing occlusion and ischemia is called as 'progressing stroke' or 'stroke in evolution'.

(I) Hemorrhagic conversion:

Ischemic stroke have a 'bland' infarction associated with secondary bleeding. This is called as hemorrhagic transformation (HT) or hemorrhagic conversion. There will be a hematoma in parenchyma with a intraventricular extension which results in herniation due to midline shift. There will be macrophage invasion and leukocyte infiltration.[66]

STROKE AND INFLAMMATION:

Inflammatory mechanism plays certain role in initiation and progression of stroke.

Inflammatory conditions:

Stroke is seen in primary angitis of CNS, SLE, Systemic sclerosis, Sarcoidosis, Inflammatory bowel disease, Giant cell arteritis, Rheumatoid arthritis.[67]

Infective conditions:

A variety of infective conditions appeared to precede stroke. Mostly are respiratory pathogens and are bacterial origin like Chlamydia pneumonia[68],

cytomegalovirus[69] and Helicobacter pylori[70], occurring within the previous month.

Inflammatory mediators:

The onset of ischemic cascade induces the initiation of inflammation, excitotoxicity, nitric oxide production, free radical damage and apoptosis, which all play a role in tissue injury. The molecular consequences due to brain ischemia include changes in cell signalling and its transduction, metabolism, gene regulation or expression.[76] There will be release cytokines, like interleukin-1(IL-1) and tumor necrosis factor-α(TNF-α) after onset of ischemia which leads to leucocyte activation, recruitment and adhesion to the endothelium.[71] These leucocytes obstruct the vessel together with monocytes /macrophages. Reperfusion, and systemic inflammatory process also stimulate the inflammatory response, which hampers the effect of thrombolytic therapy.[72]

Acute phase reactants:

In the normal conditions, the body responds to inflammatory and infective conditions, by means of cytokines, primarily IL-6 and IL-1. The most important acute phase reactants in cerebrovascular ischemia are C-reactive proteins (CRP), serum amyloid A protein, and fibrinogen.

C-reactive protein

The median CRP concentration of healthy persons is roughly 1 mg/L. Increased CRP levels predict the risk of:

(a) First episode of ischemic stroke;

(b) Future TIA and ischemic stroke and fatal stroke in the elderly.

There was a early increase in CRP within three hours of acute stroke and are therefore an independent predictor of nonfatal vascular event and survival after an ischemic stroke.[73]

Erythrocyte sedimentation rate (ESR):

Elevated ESR is an independent predictive factor of poor outcome within first month and early stroke recurrence.[74]

Fibrinogen:

There is hyperfibrinoginemia in patients with acute cerebral infarction together with leukocytosis and increased leukocyte aggregation.[75]

Body temperature:

Studies revealed that hypothermia of brain and body tends to reduce infarct size. Also that hyperthermia promotes neuronal damage. Body temperature has been related to initial stroke severity, lesion size, mortality, and outcome in stroke survivors. Raised body temperature in acute stroke, possibly due to infections has been associated with increased morbidity and mortality.[76,77]

Therapeutic intervention beyond thrombolytics:

The recent protocols for primary stroke management and secondary prevention focuses mainly on modifiable risk factors like hypertension, smoking, carotid stenosis, atrial fibrillation, physical inactivity, diabetes mellitus, and dyslipidemia, with usage of drugs like antiplatelet agents,

antihypertensive drugs, lipid-lowering agents, and anticoagulant drugs. A recent addition was intravenous tissue plasminogen activator in cases of acute ischemic stroke. Its efficacy is often limited by severity of the stroke, older age group, hypertension especially systolic, site of occlusion, collateral blood supply, and time from onset to treatment, and reperfusion-associated inflammation. The overall recanalization rate in thrombolytic therapy varies from 46.2% during the first 6–24 h of intravenous administration, to 63.2% in intraarterial and 83.6% with mechanical reperfusion techniques.[78]

Currently available agents with anti-inflammatory role:

Aspirin:

Aspirin has a direct role in modifying CRP levels, thus raising the possibility of an anti-inflammatory action apart from its antiplatelet effect mediated via COX inhibition.[79,80]

Statins[81]:

Statins reduces the incidence of ischemic stroke in patients with coronary artery disease significantly, both with and without elevated serum cholesterol concentrations. Statins have the ability to reduce CRP levels. Statins also causes plaque stabilization and even regression in some cases. It has a neuroprotective action by upregulation of endothelial NOS and inhibition of iNOS, an effect associated with augmented cerebral blood flow and reduced infarct size. Recently, Stroke Prevention by Aggressive Reduction in Cholesterol Levels

study showed that treatment with high dose atorvastatin reduced risk of stroke in patients with recent stroke and transient ischemic attack and no known coronary artery disease (CAD).[82,83]

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers:

Angiotensin II has proinflammatory effects via augmentation of expression of VCAM-1, MCP-1, and IL-6, and increased production of reactive oxygen species, which can be countered by angiotensin converting enzyme inhibitors or angiotensin II receptor blockers for having anti-inflammatory effect.[83]

Novel therapeutic agents with anti-inflammatory role:

Neuroprotective agents:

This includes a wide variety of drugs that act by restricting damage and thereby salvages the penumbral tissue. They act by excitatory neurotransmitter modulation, influx of calcium and its control. They also may be activators of metabolic pathways, antiedema drugs, adhesion of leukocyte inhibitors and free radical scavengers. Unfortunately, despite the safety and efficacy being proved by more than 100 clinical trials its translation into clinical practice remains awaited[84]. Edaravone is the first clinical neuroprotective drug which has been used for ischemic stroke from 2001 in Japan.[85] The diet rich in fruits and

vegetables have a lower cardiovascular risk, possibly due to antioxidant nutrients: vitamin C, vitamin E, beta-carotene. They inhibit LDL oxidation and also by decreases fibrinogen and there by reduces the formation of atheroma.[86]

AIM OF THE STUDY:

- To evaluate the prognostic significance of serum fibrinogen with stroke severity by correlation with clinical outcome stroke scales.

- To evaluate the correlation between serum fibrinogen and various factors in stroke patients like:
    - Age
    - sex
    - Hypertension
    - Diabetes mellitus
    - Smoking
    - Alcohol
    - Hypercholesterolemia
    - Body mass index

BACK GROUND:

SELECTION OF SUBJECTS:

Patients admitted with history of acute onset of stroke in medical wards in the Department of Medicine, Kilpauk Medical College Hospital were enrolled in after excluding the exclusion criteria.

Age and sex matched persons not having focal neurologic deficit and after verifying exclusion criteria via questionnaire were taken as controls.

INCLUSION CRITERIA:

- All patients presenting with new onset focal neurological deficit following ischemic stroke, within 48 hours of onset of stroke are taken into study.

- Patients with new onset stroke with risk factors of hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol were included.

EXCLUSION CRITERIA:

- Elderly Patients (> 80 years) were excluded.
- Individuals with associated Connective Tissue disorders and Rheumatic heart disease, Coronary Artery disease were excluded.
- Patients with chronic kidney disease, uremia were excluded.
- Patients with infective, malignant etiology for stroke were excluded.
- Patients with liver diseases like cirrhosis were excluded.
- Patients with history of Transient ischemic attacks (TIA) or Reversible ischemic neurological deficit (RIND), cerebrovascular accidents (CVA) were excluded.
- Haemorrhagic Stroke Patients (ICH, SDH) were excluded with the aid of CT scan.
- History of recent surgery and trauma.

MATERIALS AND METHODS:

Setting : Kilpauk Medical College.

Study design: prospective Cross sectional study

Period of study: 6 months from March 2013 to August 2013.

Sample size: 100 subjects (50 cases + 50 controls)

Both cases and controls are investigated by following measures.

1) A detailed medical history including present, past, family and personal history were asked.
2) General examination.
3) Vitals monitoring including blood pressure, pulse rate .
4) Body mass index.
5) Detailed neurologic examination.
6) Examination of other systems.
7) Severity score using National Institute of Health Sciences Scale at admission.
8) Complete blood count.
9) Renal function test.
10) Serum cholesterol.
11) Serum fibrinogen.
12) ECHO cardiogram.

13) CT brain plain.

14) Reassessment of morbidity and mortality using Modified Rankin's scale scores at one month follow-up.

Biochemical analysis:

After overnight fasting, blood samples were taken in the morning. Blood sugar, cholesterol and fibrinogen were measured.

The plasma fibrinogen level was measured quantitatively by Clauss method.

Principle:

Fibrinogen is a soluble plasma protein which is converted to an insoluble polymer mediated through thrombin, resulting in clot formation. This thrombin mediated clotting time of diluted plasma is inversely proportional to fibrinogen concentration of the plasma.

Test :

Venous blood is collected in an evacuated siliconized tube containing 1 volume 0.11 mol/lt of sodium citrate (3.8%) and 9 volumes of whole blood which is centrifuged for 15 minutes at RCF of 2000 g. the buffer provided in the kit is used to prepare 1: 10 dilution of patient's plasma sample.

Assay :

0.2 ml of diluted (50µl) citrated plasma is incubated for one minute then 25 µl of thrombin reagent is added at room temperature and clotting time is then determined at 37˚ C using a coagulation instrument. The fibrinogen concentration is then determined by matching the clotting time from the standard provided and prepared in the kit.

DATA ANALYSIS:

Statistical analysis:

Mean values of all parameters in subgroups were calculated by independent sample-t- test. To compare the distributions of dichotomous data viz., gender, age, smokers, presence of hypertension or diabetes and fibrinogen levels, Chi-square test was used. Association between acute ischemic stroke and fibrinogen level was assessed by logistic regression model. ANOVA test was used to assess the association between stroke scales and fibrinogen level.

All statistical analyses were performed using SPSS (software package used for statistical analysis) package. A p-value of less than 0.05 was considered to be statistically significant.

OBSERVATION ANALYSIS:

TABLE: 1. AGE WISE DISTRIBUTION AMONG CASES AND CONTROLS

AGE	CASES	CONTROLS
30-39	3	3
40-49	11	11
50-59	11	11
60-69	14	14
70-79	11	11

The minimum age of the patients in cases and controls was 35 years and the maximum age was 75 years. Among 50 cases, 6% were in 30-39 years, 22% were in 40-49 years, 22% were in 50-59 years, 28% were in 60-69 years and 22% were in 70-79 years. Likewise, among 50 controls, there were 6%, 22%, 22%, 28%, 22% in each of the above groups respectively.

CHART: 1. AGE WISE DISTRIBUTION AMONG CASES AND CONTROLS:

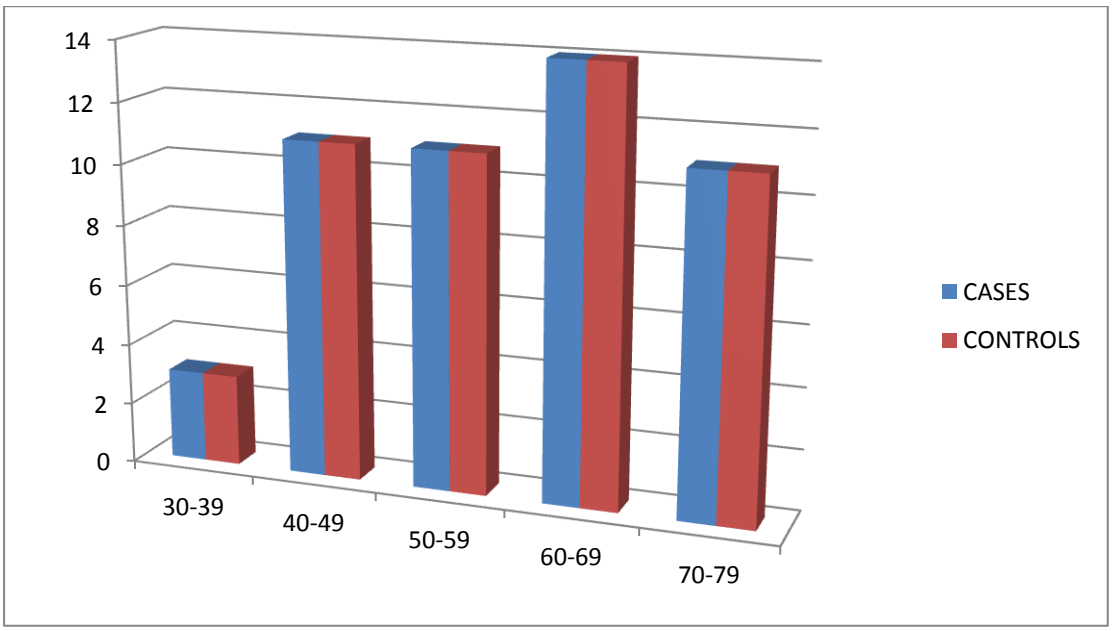


TABLE: 2. SEX DISTRIBUTION AMONG CASES AND CONTROLS

SEX	CASES	CONTROLS
MALE	31	31
FEMALE	19	19
TOTAL	50	50

The total number of cases and controls were 50 respectively. Among the cases, 31 were male and 19 were females. i.e., 62% were male among cases and 38% were female among cases. Likewise, among 50 controls, 62% (31) were males and 38% (19) were females.

CHART: 2. SEX DISTRIBUTION AMONG CASES AND CONTROLS.

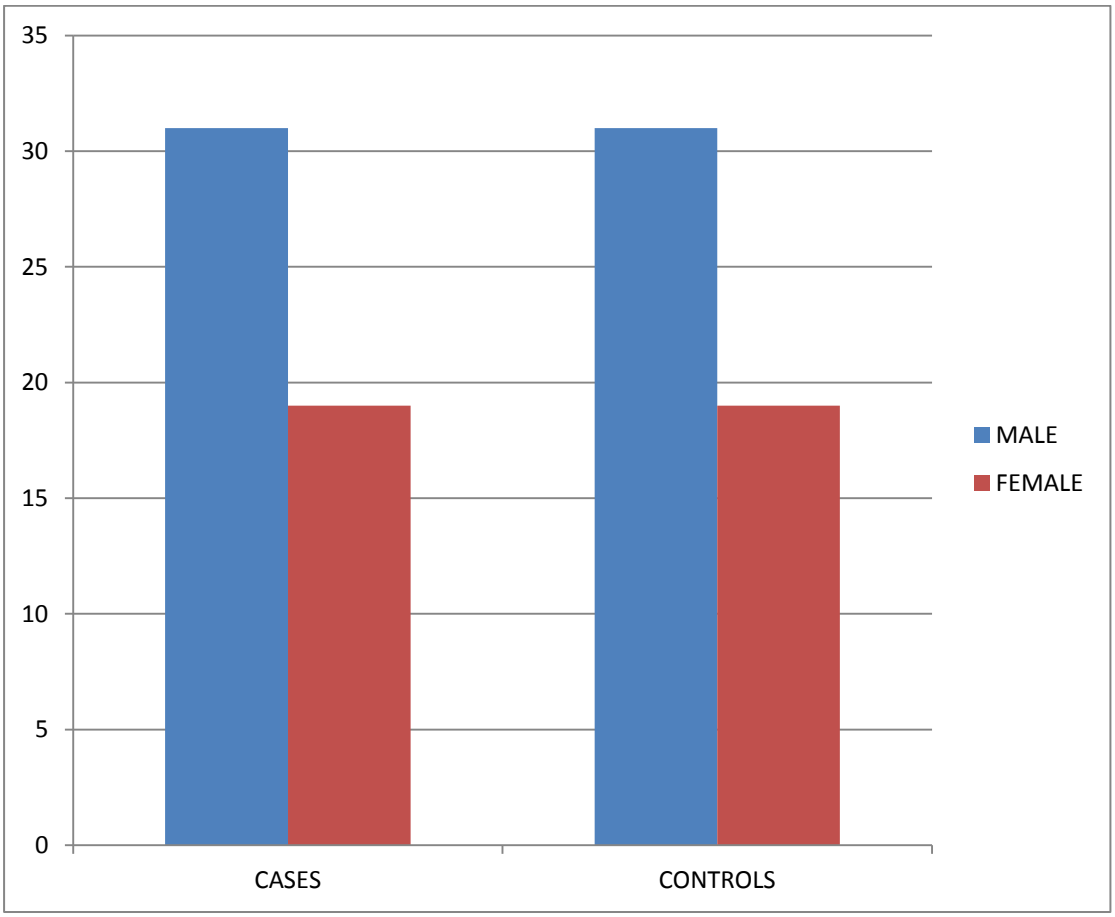


TABLE: 3. MEAN FIBRINOGEN LEVEL AMONG CASES AND CONTROLS.

	NUMBER	MEAN FIBRINOGEN	STANDARD DEVIATION	STD. ERROR OF MEAN	P-VALUE
CASES	50	612.2	186.069	26.314	
CONTROLS	50	296.8	134.854	19.071	0.001

The mean fibrinogen level among 50 cases was 612.20 mg% and the mean fibrinogen level among controls was 296.80 mg%. The p-value for mean fibrinogen between cases and controls was 0.001.

There was statistically significant difference between mean fibrinogen level between cases and controls.

CHART: 3. MEAN FIBRINOGEN LEVEL AMONG CASES AND CONTROLS

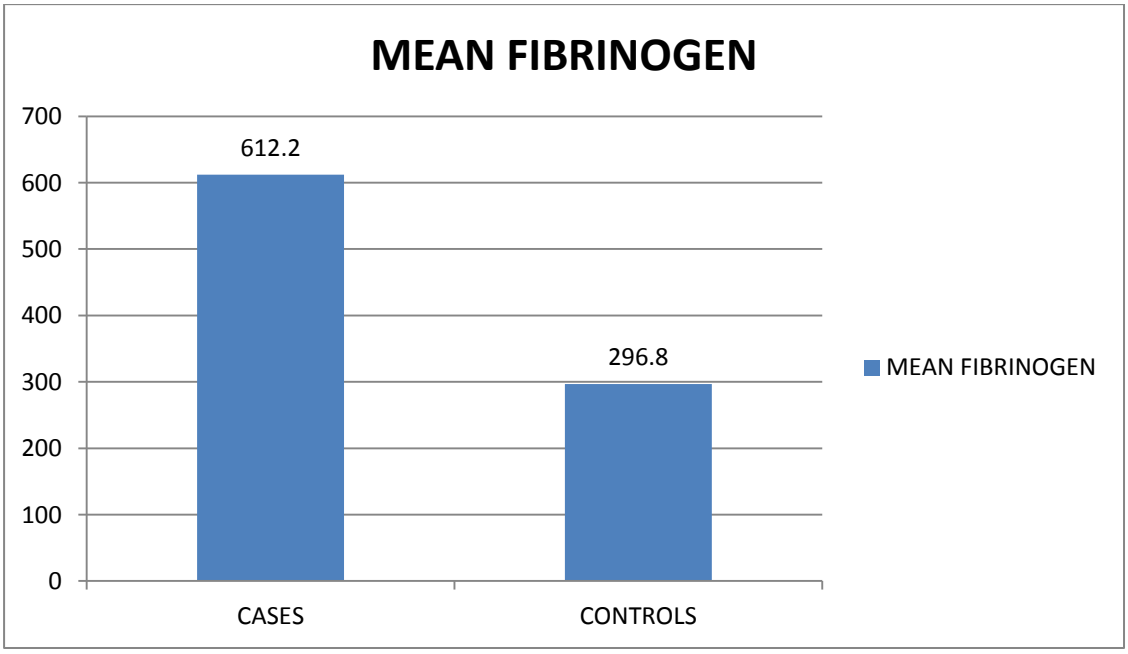


TABLE: 4. MEAN FIBRINOGEN LEVEL AMONG AGE GROUPS IN CASES AND CONTROLS

AGE IN YEARS	MEAN FIBRINOGEN						P-VALUE
	CASES			CONTROLS			
	MEAN	S.D	S.E.	MEAN	S.D.	S.E.	
30-39	520	262.3	151.438	206.67	28.87	16.667	0.109
40-49	573.64	223.93	67.518	270	92.09	27.765	0.001
50-59	599.09	186.2	56.14	308.18	124.73	37.606	0.001
60-69	631.43	179.61	48.002	312.86	166.52	44.505	0.001
70-79	664.55	145.7	43.929	316.36	157.18	47.391	0.001

The mean fibrinogen level increases as age group increases both in cases and controls. The p- value for age group 30-39 was 0.109 and for other groups it was 0.001. Therefore, there was statistically significant difference between mean fibrinogen level between cases and controls in all age groups except 30-39 years age-group, in which it was not significant.

CHART: 4. MEAN FIBRINOGEN LEVEL AMONG AGE GROUPS IN CASES AND CONTROLS

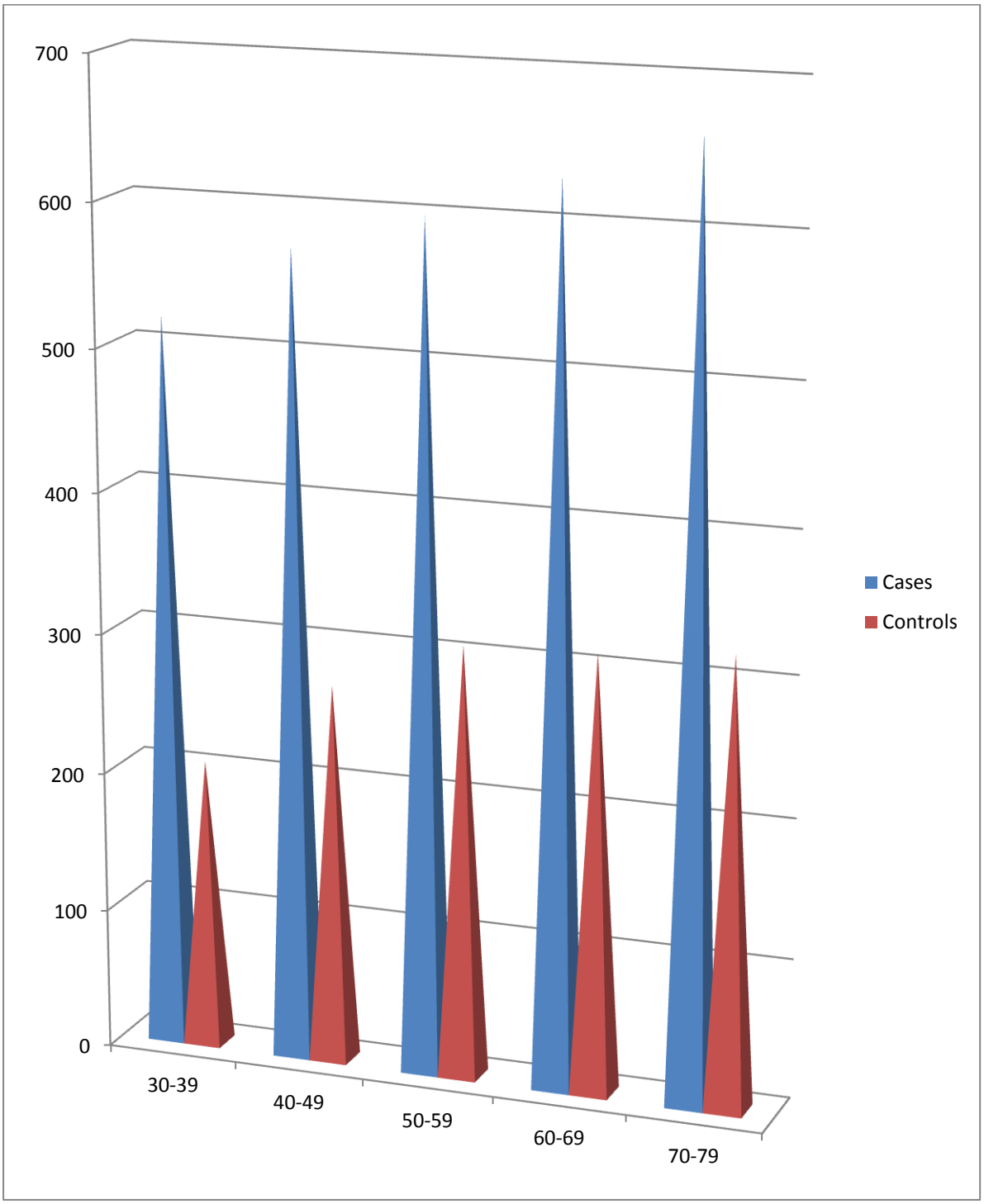


TABLE: 5. SEX WISE MEAN FIBRINOGEN LEVEL AMONG CASES AND CONTROLS.

SEX GROUP	MEAN FIBRINOGEN						P-VALUE
	CASES			CONTROLS			
	MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	
MALE	590.32	197.37	35.449	350.65	139.76	25.102	0.001
FEMALE	647.89	164.78	37.802	208.95	61.72	14.161	0.001

The mean fibrinogen level for males in cases was 590.32 and in controls it was 350.65 with a p value of 0.001.The mean fibrinogen value for females in cases was 647.89 and in controls it was 208.95 with a p-value of 0.001. Therefore, there was a statistically significant difference between mean fibrinogen level in both sexes between cases and control. But among cases, the mean fibrinogen level was greater in females than males.

CHART: 5. SEXWISE MEAN FIBRINOGEN LEVEL AMONG CASES AND CONTROLS.

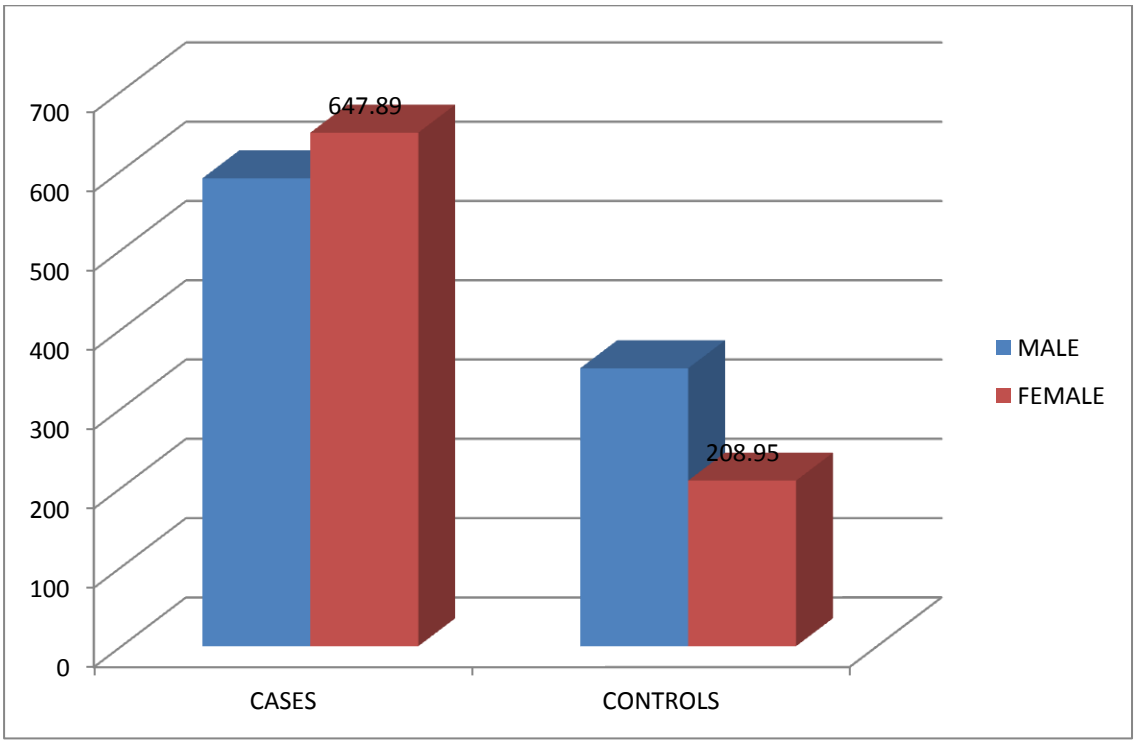


TABLE:6. NUMBER OF HYPERTENSIVES AND NORMOTENSIVES AMONG CASES AND CONTROLS.

	CASES	CONTROLS
HYPERTENSIVE	22	22
NORMOTENSIVE	28	28
TOTAL	50	50

The number of hypertensives in cases was 22 which constitutes 44% of total cases and normotensives was 28, which constitutes 56% of total 50 cases. Likewise in controls, hypertensives were 44% and normotensives were 56%.

CHART: 6. NUMBER OF HYPERTENSIVES AND NORMOTENSIVES AMONG CASES AND CONTROLS.

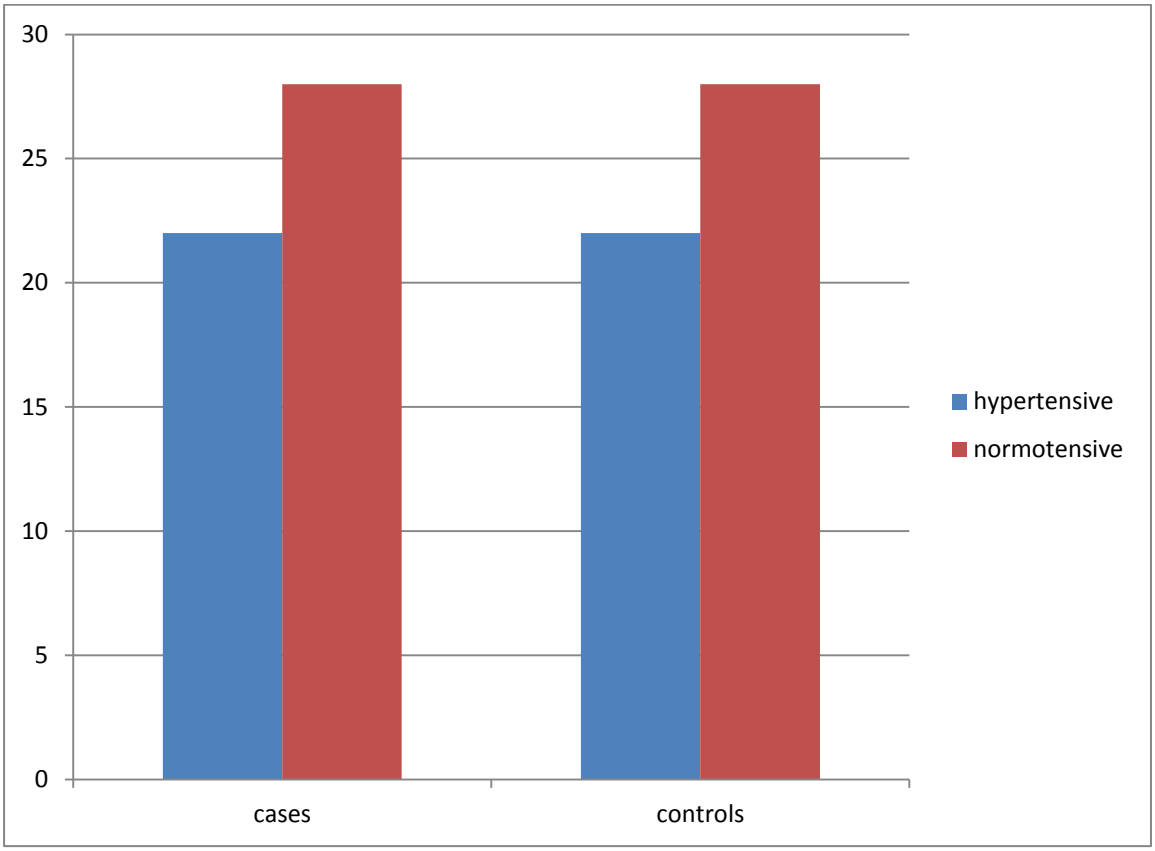


TABLE: 7. MEAN FIBRINOGEN LEVEL AMONG HYPERTENSIVES AND NORMOTENSIVES IN CASES AND CONTROLS

	MEAN FIBRINOGEN						
	CASES			CONTROLS			
	MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	P-VALUE
HYPERTENSIVE	561.36	198.67	42.356	315.45	157.23	33.522	0.001
NORMOTENSIVE	652.14	168.44	31.833	282.14	115.19	21.769	0.001

The mean fibrinogen level among hypertensives among cases was 561.36 and in controls it was 315.45 with a p- value of 0.001. The mean fibrinogen level among normotensives in cases was 652.14 and in controls it was 282.14 with a p value of 0.001. There was a statistically significant difference between mean fibrinogen level between hypertensive cases and controls, and also between normotensive cases and controls.

In cases, the mean fibrinogen level was more in normotensives than hypertensives.

CHART: 7. MEAN FIBRINOGEN LEVEL AMONG HYPERTENSIVES AND NORMOTENSIVES IN CASES AND CONTROLS.

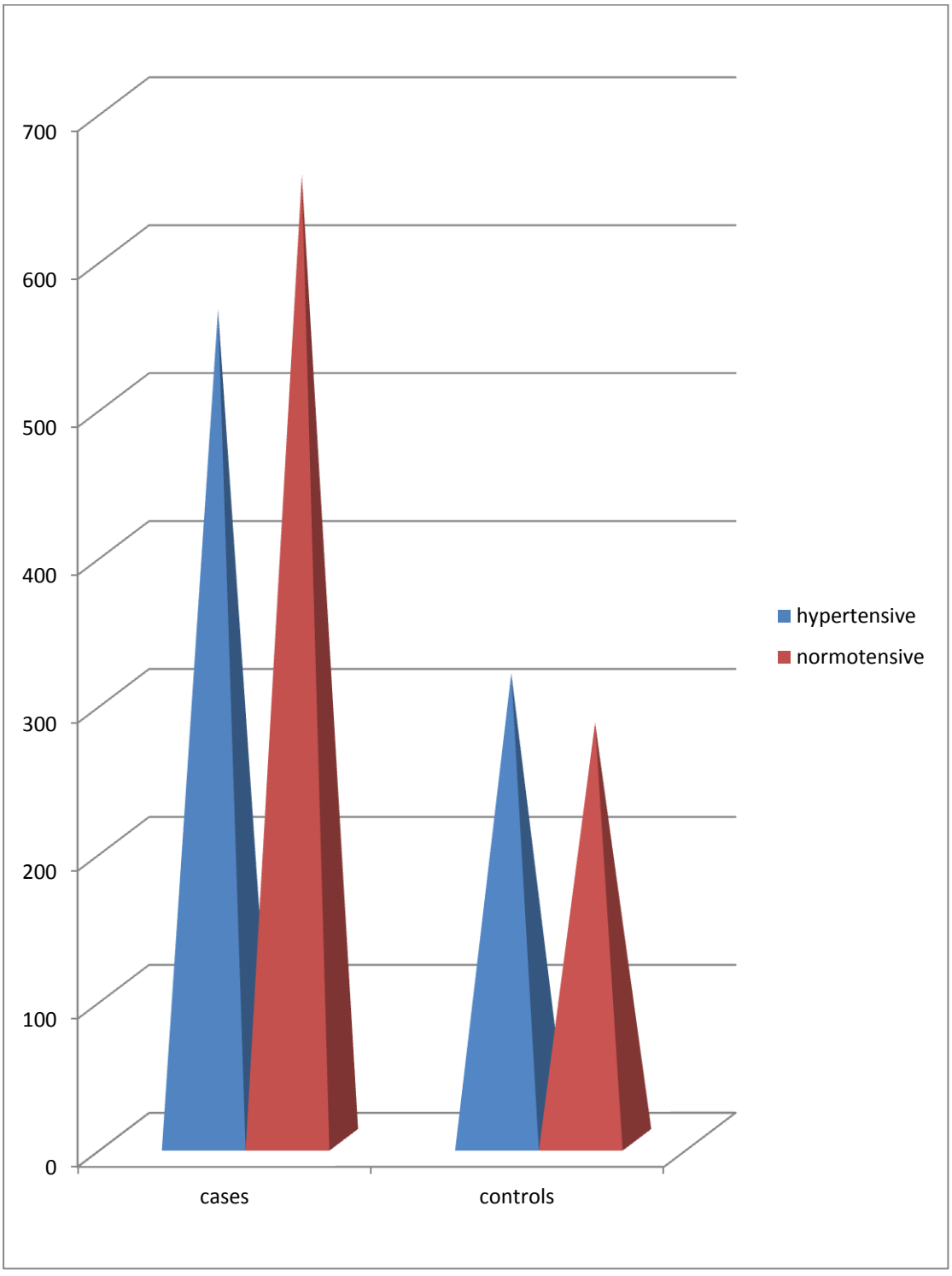


TABLE: 8. NUMBER OF PERSONS WITH DIABETES AMONG CASES AND CONTROLS.

	CASES	CASES
DIABETES	15	15
NON-DIABETES	35	35
TOTAL	50	50

Among 50 cases, 30% i.e., 15 were having diabetes and 70% (35) not having diabetes. Likewise, among 50 controls, 30% were diabetics and 70% were non-diabetics.

CHART: 8. NUMBER OF DIABETICS AMONG CASES AND CONTROLS.

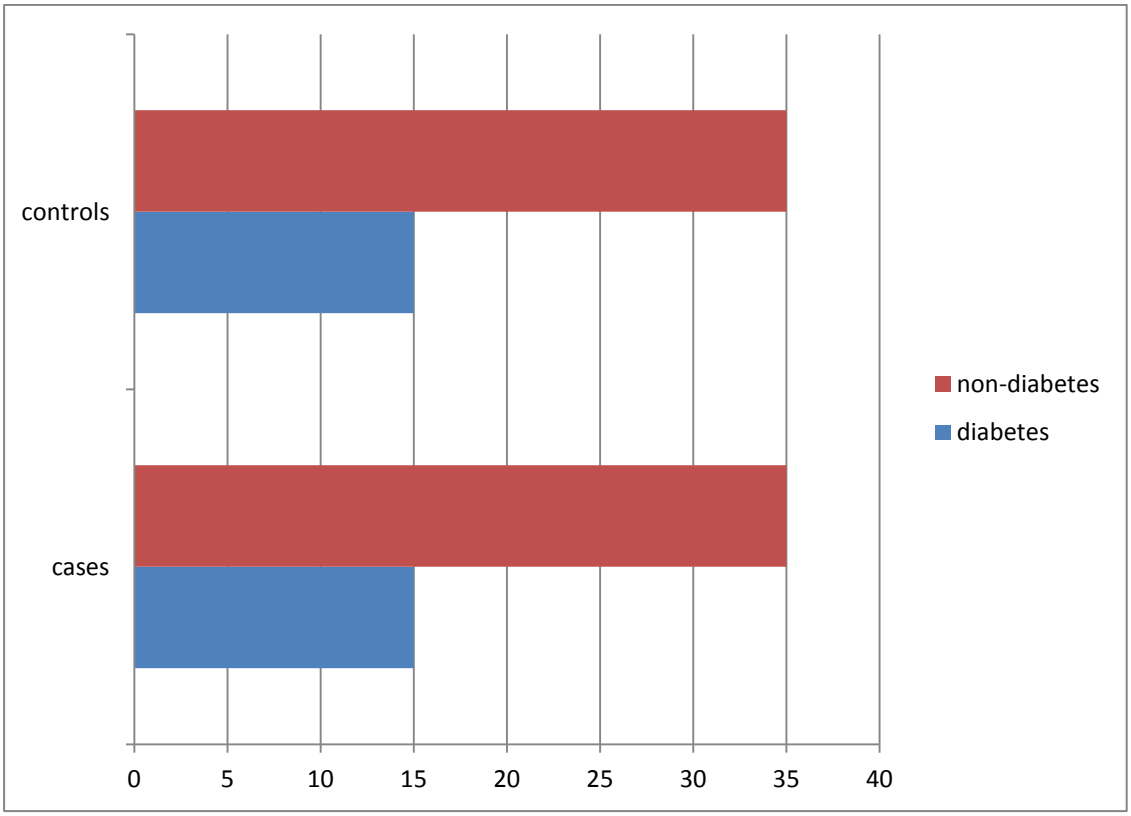


TABLE:9. MEAN FIBRINOGEN LEVEL AMONG DIABETICS AND NON-DIABETICS IN CASES AND CONTROLS.

	MEAN FIBRINOGEN						
	CASES			CONTROL			
	MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	P-VALUE
DIABETES	542.67	209.91	54.2	272.67	133.5	34.468	0.001
NON-DIABETES	642	169.42	28.638	307.14	136.03	22.993	0.001

The mean fibrinogen level among diabetics in cases was 542.67 which is higher than the mean fibrinogen for diabetics in control,which was 272.67 with a p- value of 0.001 and it was statistically significant.

Similarly, the mean fibrinogen level among non-diabetics in cases was 642 and in controls was 307.14 with a p- value of 0.001, which was statistically significant. Among cases and controls, the mean fibrinogen level was higher in non-diabetics than diabetics.

CHART: 9. MEAN FIBRINOGEN LEVEL AMONG DIABETICS AND NON-DIABETICS IN CASES AND CONTROLS.

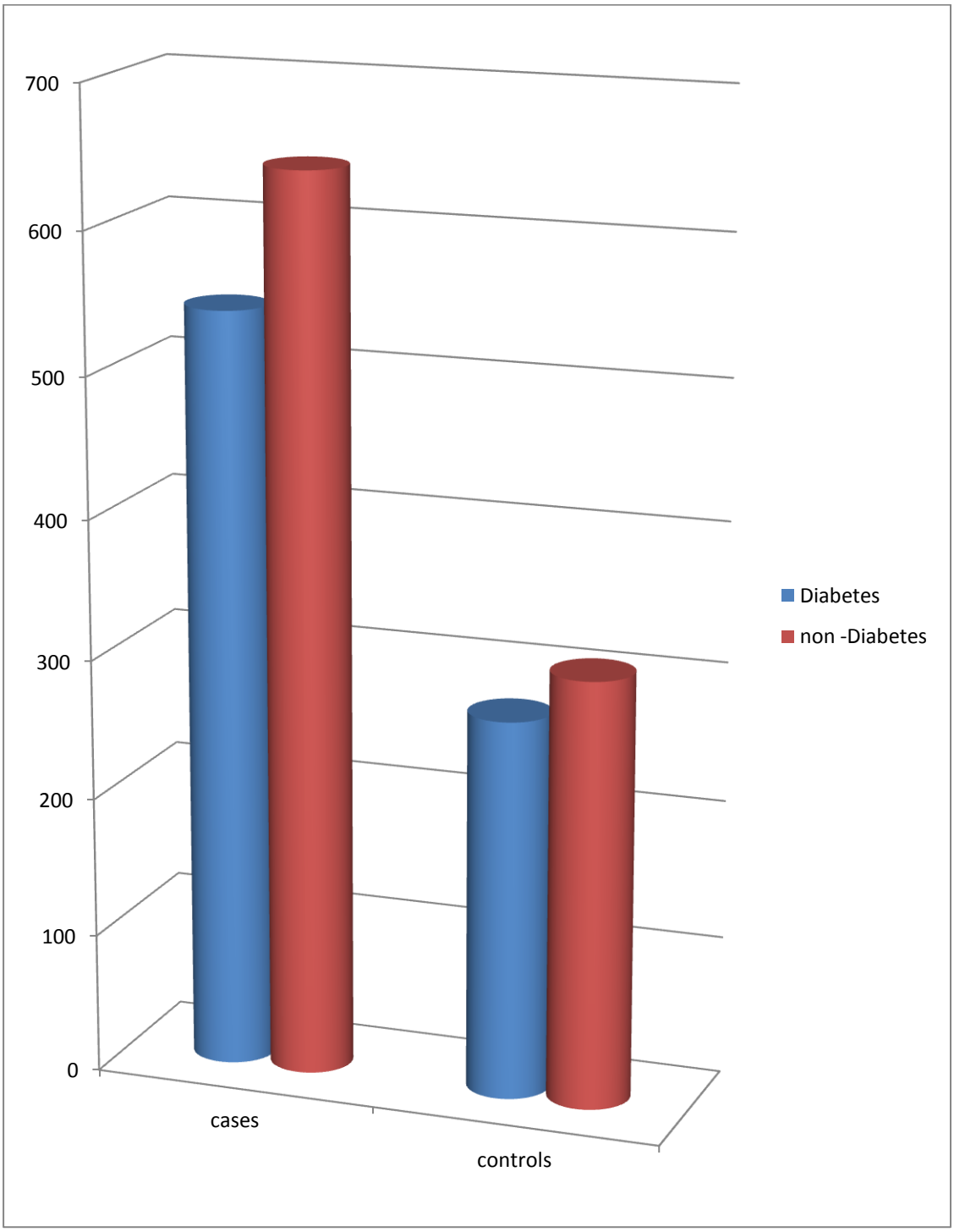


TABLE:10. NUMBER OF SMOKERS AND NON-SMOKERS AMONG CASES AND CONTROLS

	CASES	CONTROLS
SMOKERS	23	23
NON-SMOKERS	27	27
TOTAL	50	50

Among the 50 cases, 46% (23) were smokers and 54% (27) were non-smokers. Among the 50 controls, 46% were smokers and 54% were non-smokers.

CHART:10. NUMBER OF SMOKERS AND NON-SMOKERS AMONG CASES AND CONTROLS.

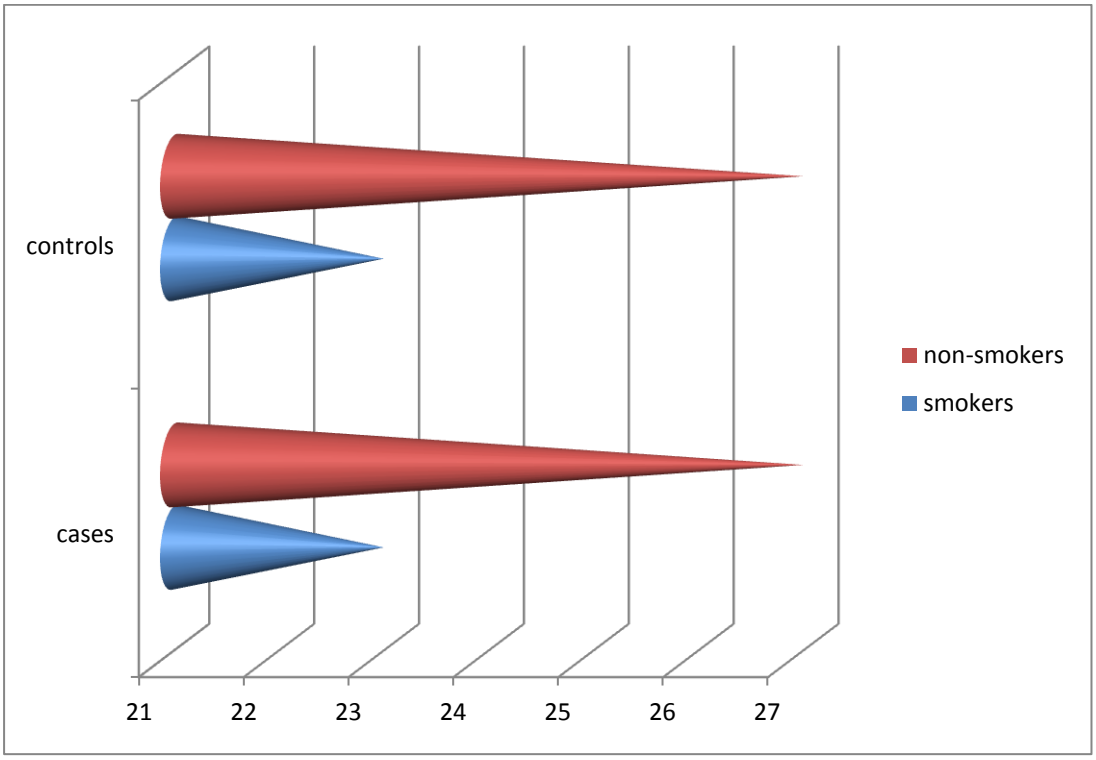


TABLE: 11. MEAN FIBRINOGEN LEVEL AMONG SMOKERS AND NON-SMOKERS IN CASES AND CONTROLS.

	MEAN FIBRINOGEN						
	CASES			CONTROLS			
	MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	P-VALUE
SMOKER	594.78	202.84	42.295	332.17	148.05	30.87	0.001
NON-SMOKER	627.04	173.02	33.298	266.67	116.95	22.507	0.001

The mean fibrinogen level among smokers in cases was 594.78 and the mean fibrinogen level among smokers in controls was 332.17 with a p-value of 0.001.

Similarly, the mean fibrinogen level among non-smokers in cases was 627.04 and non-smokers in controls was 266.67 with a p-value of 0.001.

Therefore, there was a statistically significant difference between mean fibrinogen levels both among smokers and non-smokers between cases and controls.

CHART: 11. MEAN FIBRINOGEN LEVEL AMONG SMOKERS AND NON-SMOKERS IN CASES AND CONTROLS.

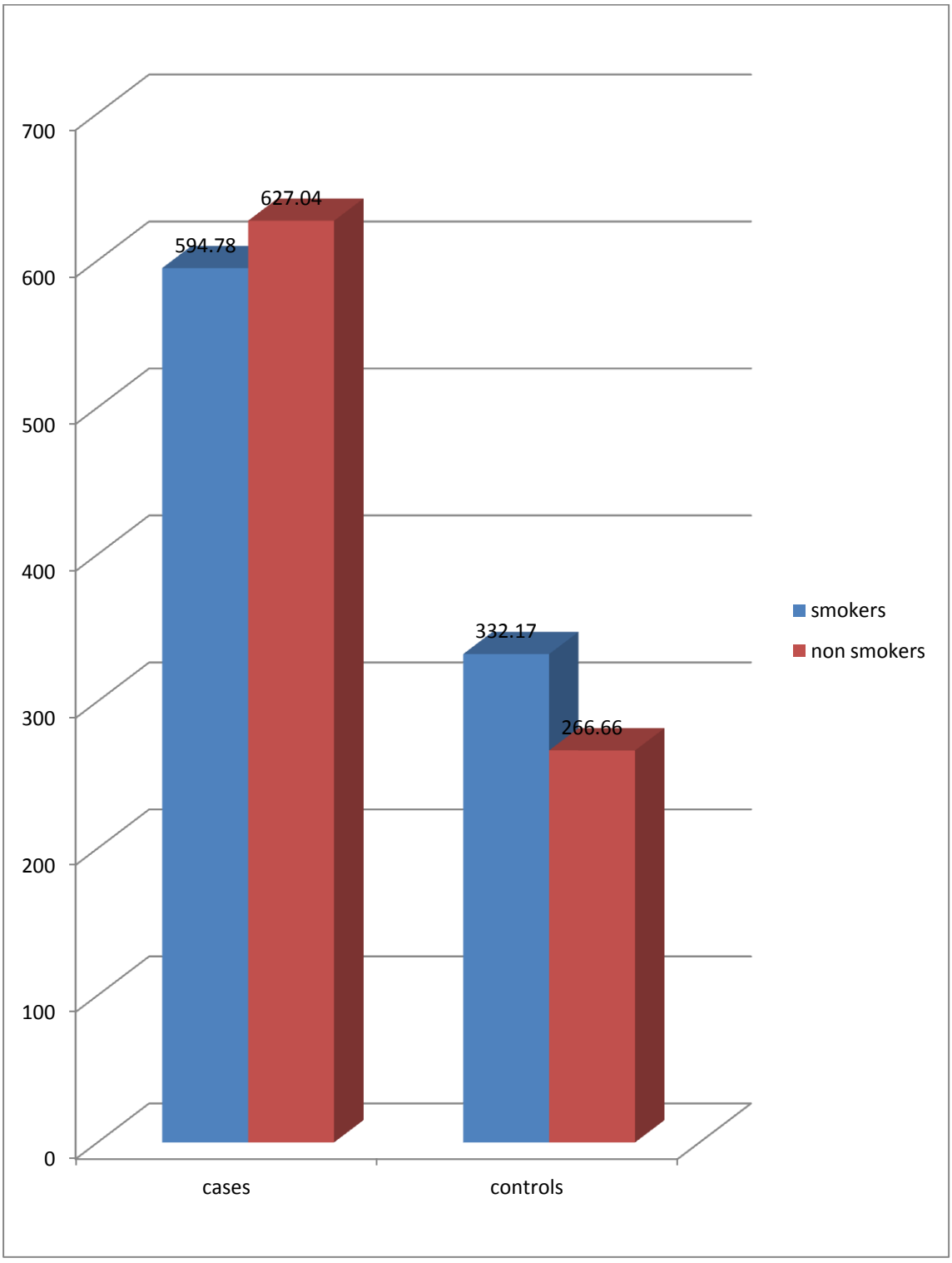


TABLE: 12. NUMBER OF ALCOHOLICS AND NON-ALCOHOLICS AMONG CASES AND CONTROLS.

	CASES	CONTROLS
ALCOHOLICS	14	14
NONALCOHOLICS	36	36
TOTAL	50	50

Among the 50 cases, 28% (14) were alcoholics and 72% (36) were non-alcoholics. Likewise, among 50 controls, 28% (14) were alcoholics and 72% (36) were non-alcoholics.

CHART: 12. NUMBER OF ALCOHOLICS AND NON-ALCOHOLICS AMONG CASES AND CONTROLS.

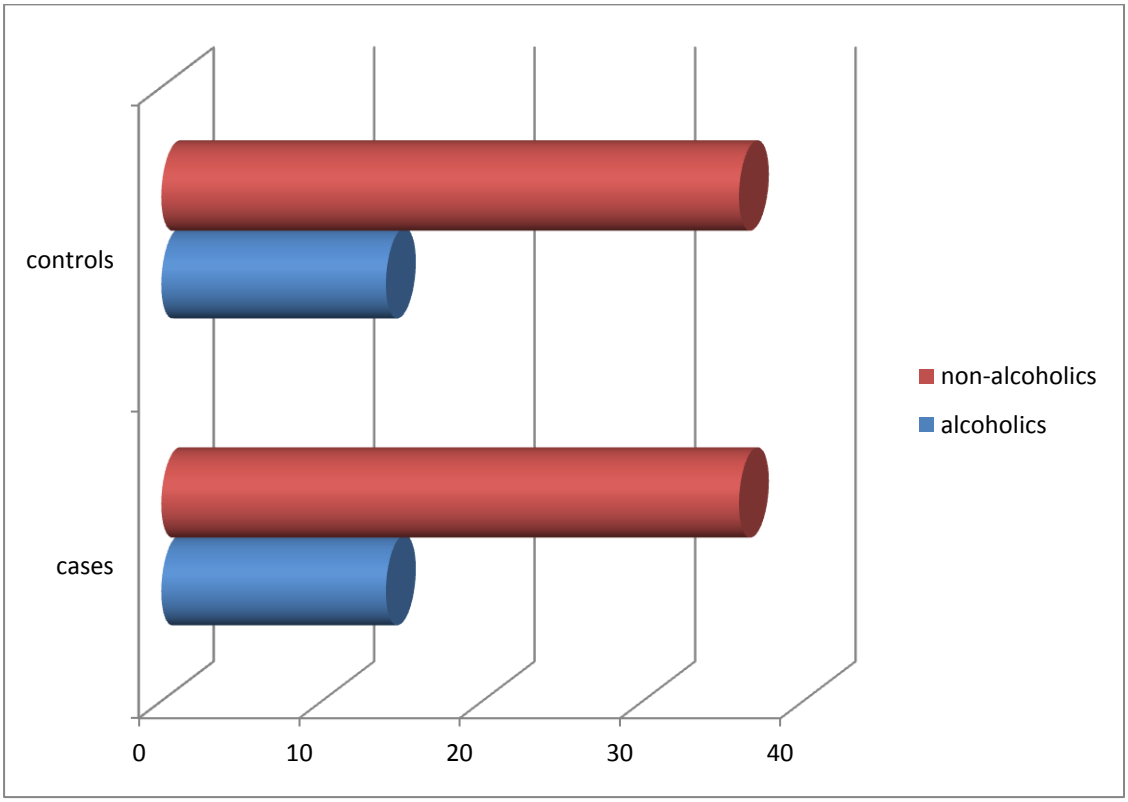


TABLE: 13. MEAN FIBRINOGEN LEVEL AMONG ALCOHOLICS AND NON-ALCOHOLICS IN CASES AND CONTROLS.

	MEAN FIBRINOGEN						
	CASES			CONTROLS			
	MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	P-VALUE
ALCOHOL	577.14	188.08	50.268	328.57	133.06	35.562	0.001
NON-ALCOHOL	625.83	186.14	31.023	284.44	135.36	22.56	0.001

The mean fibrinogen level among alcoholics in cases was 577.14 and the mean fibrinogen level among alcoholics in controls was 328.57 with a p-value of 0.001.

Similarly, the mean fibrinogen level among non-alcoholics in cases was 625.83 and the mean fibrinogen level among non-alcoholics in controls was 284.44 with a p-value of 0.001.

Therefore, there was a statistically significant difference between mean fibrinogen level both among alcoholics and non-alcoholics between cases and controls.

CHART: 13. MEAN FIBRINOGEN LEVEL AMONG ALCOHOLICS AND NON- ALCOHOLICS IN CASES AND CONTROLS.

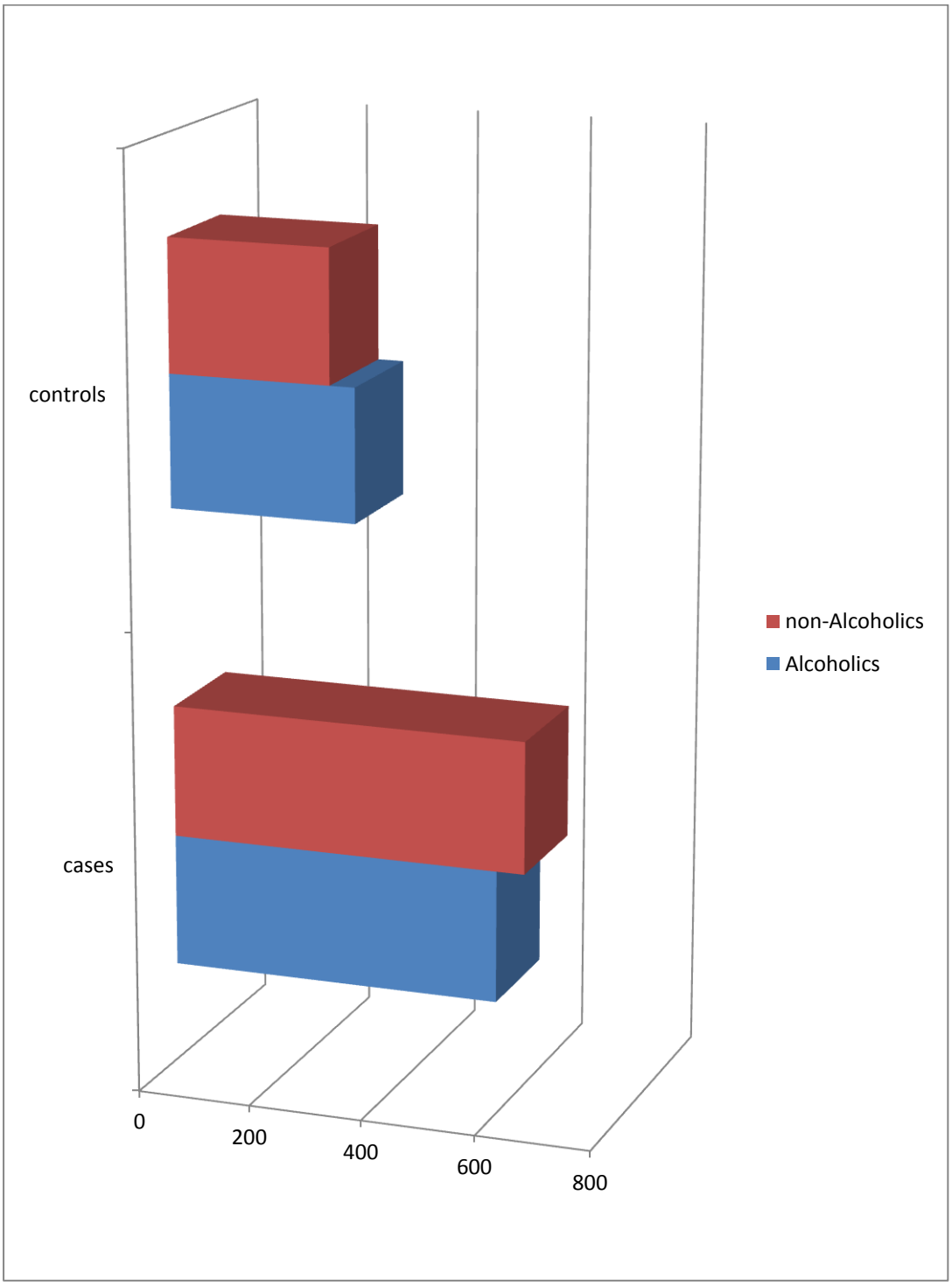


TABLE:14. NUMBER OF OBESE AND NON-OBESE PERSONS AMONG CASES AND CONTROLS.

	CASES	CONTROLS
OBESE	25	25
NON-OBESE	25	25
TOTAL	50	50

Among, the 50 cases, 25 (50%) were obese and 25 (50%) were non-obese. Likewise in 50 controls, 50% were obese and 50% were non- obese.

CHART: 14. NUMBER OF OBESE AND NON-OBESE AMONG CASES AND CONTROLS.

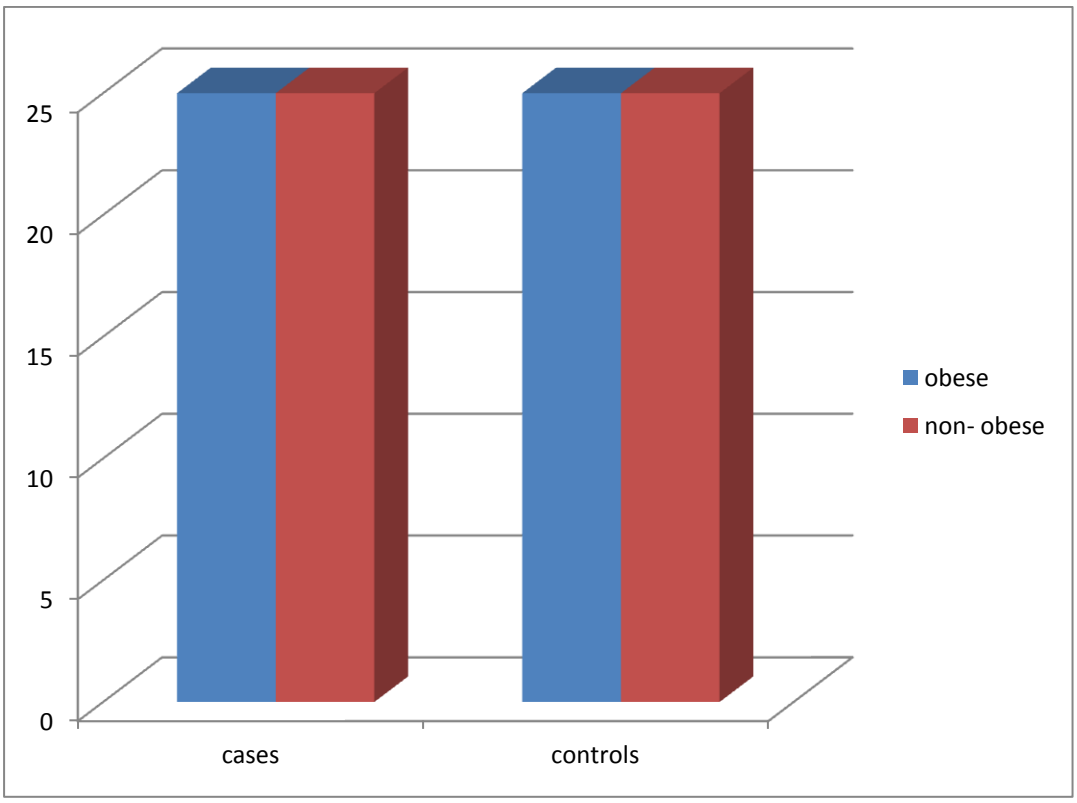


TABLE: 15. MEAN FIBRINOGEN LEVEL AMONG OBESE AND NON-OBESE IN CASES AND CONTROLS.

	MEAN FIBRINOGEN						
	CASES			CONTROLS			
	MEAN	S.D.	STD. ERROR	MEAN	S.D.	STD. ERROR	P-VALUE
OBESE	733.6	57.146	11.429	312	131.846	26.369	0.001
N0N-OBESE	490.8	191.614	38.323	281.6	138.795	27.759	0.001

The mean fibrinogen level among obese in cases was 733.60 and the mean fibrinogen level among obese in controls was 312 with a p-value of 0.001.

Similarly, the mean fibrinogen level among non-obese in cases was 490.8 and mean fibrinogen level among non-obese in controls was 281.60 with a p-value of 0.001.

Therefore, there was a statistically significant difference between mean fibrinogen level both among obese and non- obese between cases and controls.

CHART: 15. MEAN FIBRINOGEN LEVEL AMONG OBESE AND NON-OBESE IN CASES AND CONTROLS.

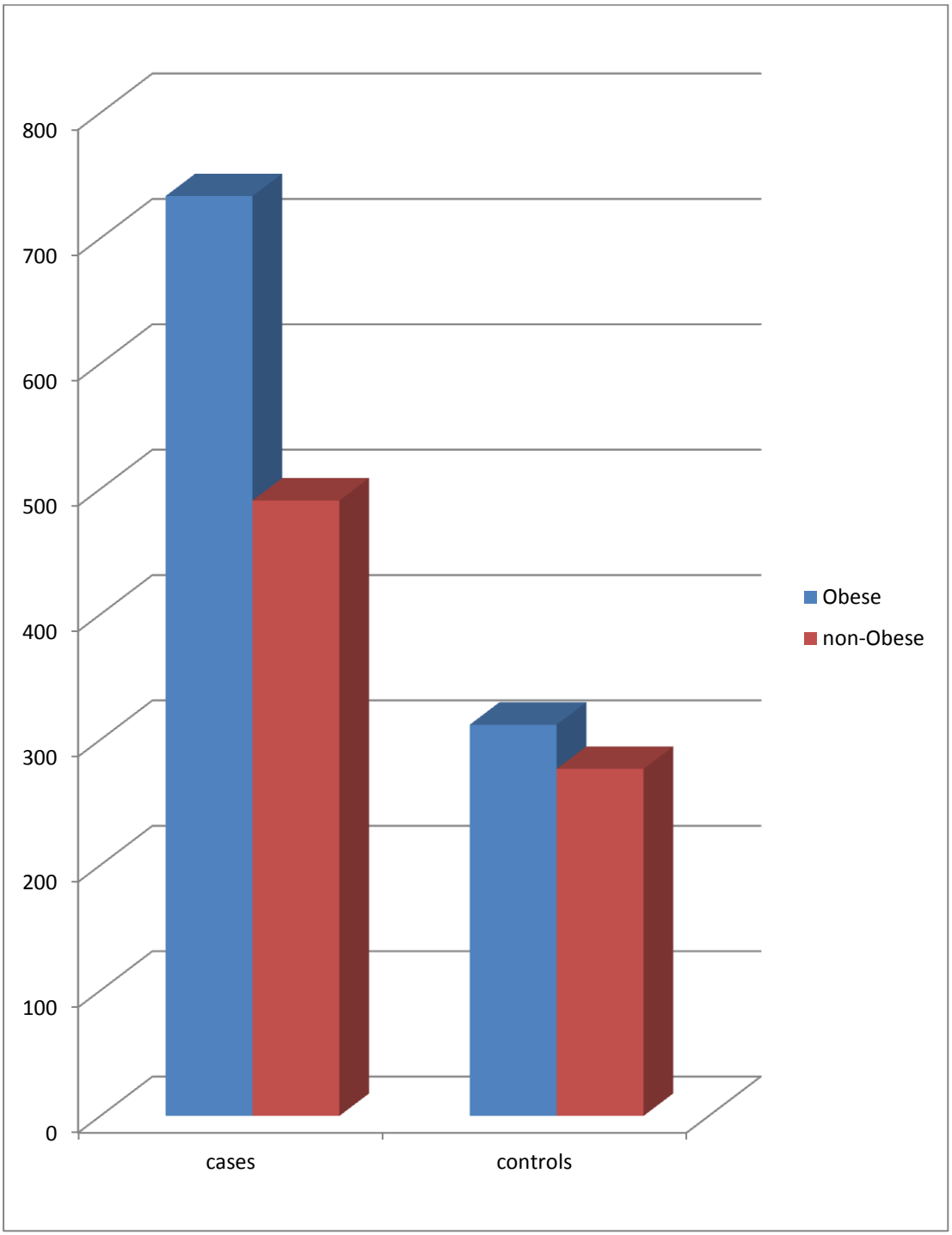


TABLE:16. NUMBER OF PERSONS WITH HYPERCHOLESTEROL AND NORMAL CHOLESTEROL AMONG CASES AND CONTROLS.

	CASES	CONTROLS
HYPERCHOLESTEROL	30	30
NORMAL CHOLESTEROL	20	20
TOTAL	50	50

Among 50 cases, 60% (30) had hypercholesterol and 40% (20) had normal cholesterol levels. Likewise, 30 (60%) in controls had hypercholesterol and 20 (40%) had normal cholesterol.

CHART: 16. NUMBER OF PERSONS WITH HYPERCHOLESTEROL AMONG CASES AND CONTROLS.

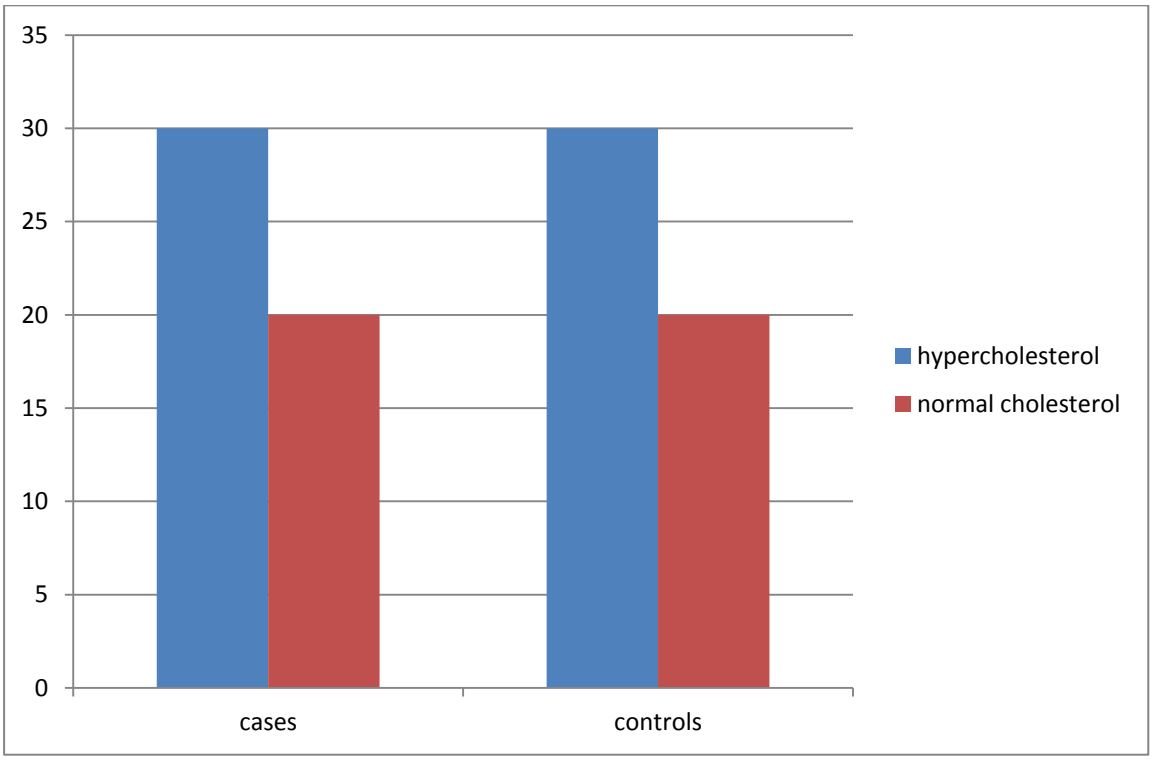


TABLE:17. MEAN FIBRINOGEN LEVEL AMONG PERSONS WITH HYPERCHOLESTEROL AND NORMAL CHOLESTEROL IN CASES AND CONTROLS.

	MEAN FIBRINOGEN						
	CASES			CONTROLS			
	MEAN	S.D.	STD. ERROR	MEAN	S.D.	STD. ERROR	P-VALUE
HYPERCHOLESTEROL	662	164.283	43.763	304.67	128.378	23.439	0.001
NORMAL CHOLESTEROL	537.5	195.714	43.763	285	146.629	32.787	0.001

The mean fibrinogen level among patients with hypercholesterol in cases was 662 and in controls was 304.67 with a p-value of 0.001.

Similarly, the mean fibrinogen level among patients with normal cholesterol in cases was 537.5 and in controls was 285 with a p-value of 0.001.

Therefore, there was a statistically significant difference between mean fibrinogen level both among persons with hypercholesterol and normal cholesterol between cases and controls.

CHART: 17. MEAN FIBRINOGEN LEVEL AMONG PERSONS WITH HYPERCHOLESTEROL AND NORMAL CHOLESTEROL IN CASES AND CONTROLS.

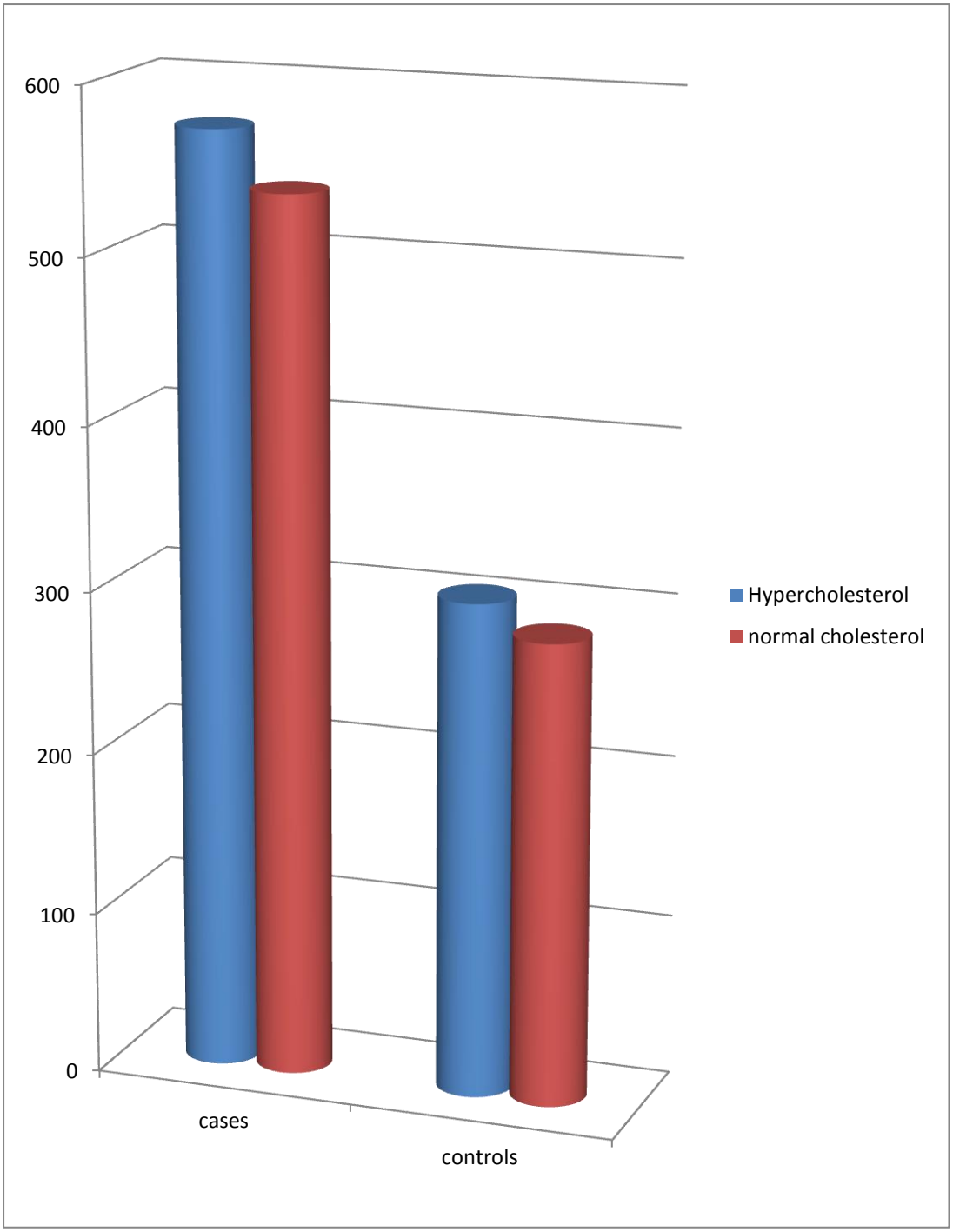


TABLE:18. NIHSS SCORE AMONG CASES AND THEIR MEAN FIBRINOGEN LEVEL.

NIHSS SCORE	NUMBER	MEAN FIBRINOGEN		
		MEAN	S.D.	STD. ERROR
MILD(<5)	10	312	110.635	34.986
MODERATE(6-15)	13	560	93.452	25.919
SEVERE (16-25)	10	710	11.547	3.651
VERY SEVERE(>25)	17	771.18	33.89	8.22

The severity of ischemic stroke was graded using National Institute of Health Stroke Scale score during admission. Based on the scores, the cases were classified as mild (score < 5), moderately severe (score 6 - 15), severe (score 16 – 25) and very severe (score > 25).

Among the cases, 10 had mild stroke, 13 had moderately severe stroke, 10 had severe stroke and 17 had very severe stroke.

The mean fibrinogen level among mild cases was 312. The mean fibrinogen among moderately severe cases was 560. The mean fibrinogen level among severe cases was 710 and the mean fibrinogen level among very severe cases was 771.18.

Hence, it was obvious that the stroke severity increases with increased fibrinogen levels in cases during admission.

CHART: 18. NIHSS SCORE AMONG CASES AND THEIR MEAN FIBRINOGEN LEVEL.

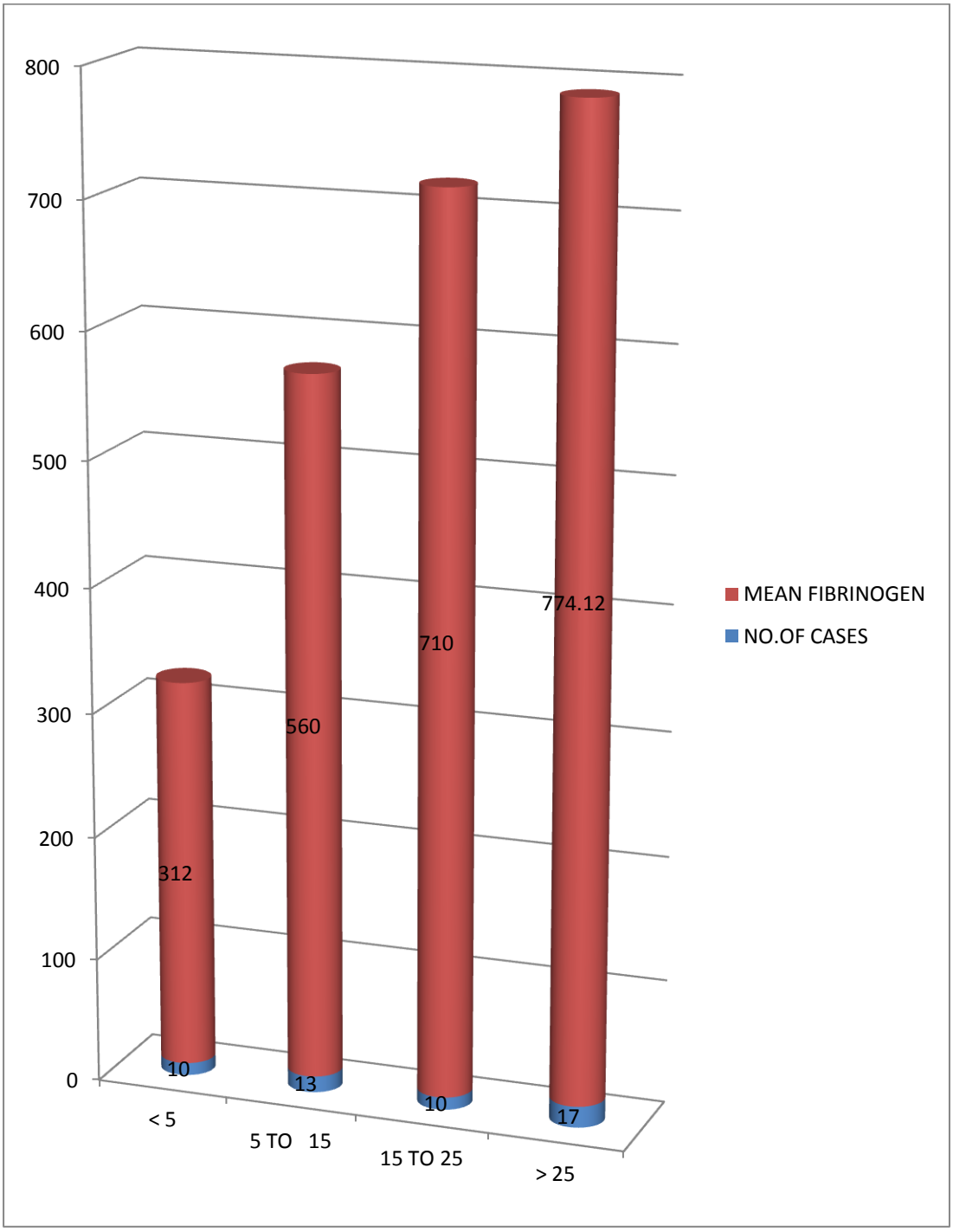


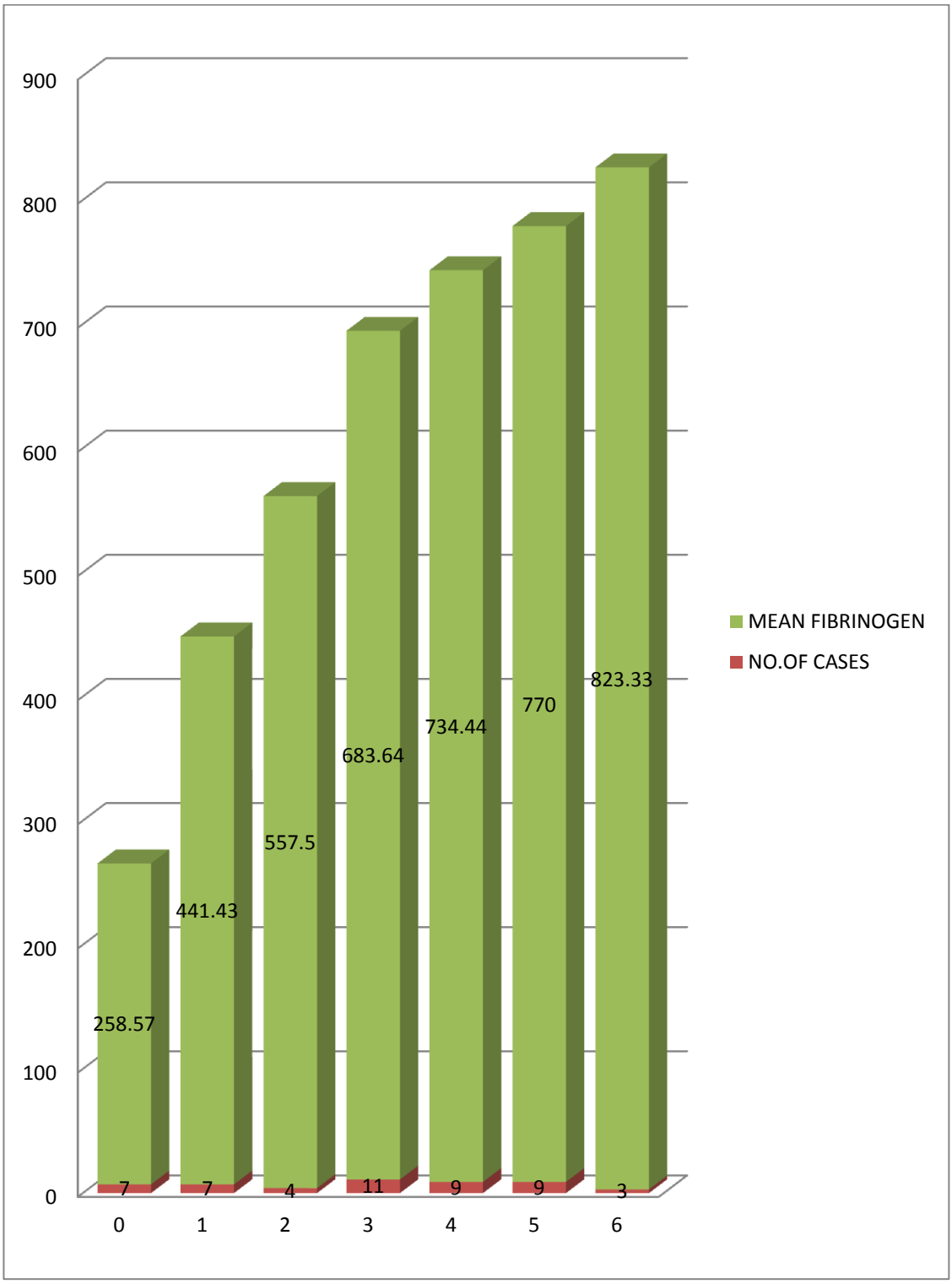
TABLE: 19. MODIFIED RANKIN'S SCALE SCORE AT 1 MONTH AMONG CASES AND THEIR MEAN FIBRINOGEN LEVEL.

MRS SCORE AT 1 MONTH	NUMBER	MEAN FIBRINOGEN		
		MEAN	S.D.	STD. ERROR
0	7	258.57	83.95	31.73
1	7	441.43	32.367	12.234
2	4	557.5	5	2.5
3	11	683.64	33.548	10.115
4	9	734.44	22.423	7.474
5	9	764.44	25.55	8.517
6	3	823.33	37.859	21.858

The cases were followed up for one month and the morbidity and mortality were assessed using Modified Rankin's Scale at one month after the stroke onset. Based on the morbidity, the cases were assigned scores from 0 to 6(0 for no symptoms and 6 for death).

Among the 50 cases, 7 cases with mean fibrinogen level of 258.57 had no symptoms (score 0), another 7 cases with mean fibrinogen level of 441.43 had no significant disability despite symptoms (score1), 4 cases with mean fibrinogen level of 557.50 had slight disability (score 2), 11 cases with mean fibrinogen level of 683.64 had moderately severe disability (score 3), 9 cases with mean fibrinogen level of 734.44 had severe disability (score 4), another 9 with mean fibrinogen level of 764.44 had very severe disability (score 5) and 3 cases with mean fibrinogen level of 823.33 were dead (score 6). Hence, the severity and prognosis of stroke were worse with increased fibrinogen levels during admission.

CHART: 19. MODIFIED RANKIN'S SCALE SCORE AT 1 MONTH AMONG CASES AND THEIR MEAN FIBRINOGEN LEVEL.



DISCUSSION:

A total of 100 patients were enrolled in our study which comprises of 50 patients with acute ischemic stroke (study group) and 50 persons without stroke (control group).

The mean age of study group was 57.72 with a standard deviation of 11.898 and standard error of mean of 1.683. the mean age of control group was 57.64 with standard deviation of 11.955 and standard error of mean of 1.691. There was no statistical difference in the two groups ($p > 0.05$) regarding the baseline characteristics such as age, sex, diabetes, hypertension, smoking, alcohol, obesity and hypercholesterolemia. The two groups were statistically matched regarding baseline characteristics.

FIBRINOGEN LEVEL BETWEEN CASES AND CONTROL GROUP:

The mean fibrinogen level among cases was 612.20 with a standard deviation of 186.069 and standard error of mean 26.314.

Likewise, the mean fibrinogen level among control group was 296.80 with standard deviation of 134.854 and standard error of mean 19.071, with a p value of 0.001 (< 0.05) which was statistically significant.

SI.NO	STUDY	STUDY POPULATION	MEAN FIBRINOGEN		P-VALUE
			CASES	CONTORLS	
1	HAZRA B ET AL	63 PATIENTS, 30 CONTOLS	378.67	216.67	<0.01
2	MISTRY P ET AL	56 PATIENTS, 40 CONTROLS	534±74	445.78±92.28	<0.01
3	AMITH KUMAR ET AL	50 CASES , 50 CONTROLS	602±197.2463	301±141.4538	<0.05
4	OUR STUDY	50 CASES , 50 CONTROLS	612.2	296.8	0.001

Similar to the above studies, the current study also demonstrated a significant increase in serum fibrinogen levels in ischemic stroke patients when compared with controls. Hazra B et al, Amith kumar et al studies include patients with both ischemic and hemorrhagic stroke in study group whereas current study includes only ischemic stroke patients.

The study group comprises of 50 patients with acute ischemic stroke. Among the study group, 44% (22) were hypertensive, 30% (15) were diabetics, 46% (23) were smokers, 28% (14) were alcoholics, 50% (25) were obese, 60% (30) were having hypercholesterolemia.

The mean fibrinogen level in the study group increases as age advances, which was higher than that of control group, with a p- value of 0.001 which was statistically significant.

The mean fibrinogen level among males and females in study group was higher than control group which was statistically significant ($p<0.05$).

In the study group, the mean fibrinogen level of hypertensive, diabetic, smokers, alcoholic, obese and hypercholesterolic patients were higher than that of seen in control groups, which was statistically significant.

Likewise, the mean fibrinogen level of normotensive, non diabetic, non smokers, non alcoholics, non obese and normal cholesterol patients in study group were higher than that of control group which was also statistically significant ($p<0.05$).

The mean fibrinogen level is higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score <5.

The mean fibrinogen level in mild impairment cases was 312, moderately severe cases was 560, severe cases was 710 and very severe cases was 771.18. Hence, it was clear that the fibrinogen levels were higher in patients with acute ischemic stroke with very severe impairment.

After one month of acute ischemic stroke onset, the morbidity and mortality were assessed using Modified Rankin's Scale (MRS). It was found that the outcome was worse in cases with higher fibrinogen levels. There were 3 dead with a MRS score of 6 and mean fibrinogen level of 823.33.

The mean fibrinogen level in patients with no symptoms at one month after stroke onset was 258.57 (MRS score 0). The mean fibrinogen level in

patients with MRS score of 1 was 441.43 and they had no significant disability despite symptoms. The mean fibrinogen level in patients with slight disability (MRS score2) was 557.50. The mean fibrinogen level for MRS score of 3, 4 and 5 were 683.64, 734.44 and 764.44 respectively.

Hence, it was clear that among the cases, the acute ischemic stroke was very severe in patients with higher fibrinogen levels. Also, the outcome at the end of one month was poor in patients with higher fibrinogen levels during stroke onset.

CONCLUSION:

1. Serum fibrinogen level was higher in patients with acute ischemic stroke compared to controls.
2. Among the patients with acute ischemic stroke, the higher serum fibrinogen level correlates with:
    a. Clinical severity assessed by National Institute Of Health Stroke Scale.
    b. Poor prognosis and stroke outcome at end of one month after stroke onset, assessed by Modified Rankin's Scale.

CLINICAL SIGNIFICANCE:

Fibrinogen is associated with risk factors for stroke. Therefore, elevated fibrinogen levels provide a mechanism for the risk factors to exert their effect. Fibrinogen is increased following an acute stroke as an acute phase reactant. Also, fibrinogen predicts vascular events in established atherosclerotic disorders. Hence, chronically raised fibrinogen in high risk individuals appears to be an independent risk factor for stroke.

Measures such as cessation of smoking, weight reduction, increased physical activity and control of blood pressure decreases plasma fibrinogen level, thereby reduces stroke occurrence in high risk individuals in future.

Therefore, plasma fibrinogen measurement can be used as a screening for at risk persons for stroke and other vascular events and also as a prognostic marker following an acute stroke. The measures to decrease plasma fibrinogen levels can be included in preventive strategies against stroke.

ANNEXURES

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PROFORMA

NAME:

AGE:

SEX:

OCCUPATION:

IP.No.:

RISK FACTORS: YES/NO

1. SYSTEMIC HYPERTENSION
2. DIABETES MELLITUS
3. SMOKING
4. ALCOHOL
5. IHD
6. RHD
7. AF
8. PREVIOUS HISTORY OF STROKE
9. HIGH CHOLESTEROL

SIGNS:

GENERAL

Built: Pallor: Icterus:

Pedal oedema: Fever: cyanosis:

Clubbing: PR: BP:

BMI :

SYSTEM EXAMINATION:

CVS:

RS :

PER ABDOMEN:

CNS:

SYMPTOMS:

1. HEAD ACHE +/-

2. VOMITING +/-

3. LOSS OF CONSCIOUSNESS +/-

4. GIDDINESS +-

5. CONVULSIONS +/-

6. GAIT DISTURBANCES +/-

7. SPEECH DISTURBANCES +/-

SIGNS:

1. DIPLOPIA +/-

2. SPEECH DEFICIT +/-

3. CRANIAL NERVE INVOLVMENT

4. MOTOR DEFICIT

5. SENSORY DEFICIT

6. CEREBELLAR SIGNS

7. NIHSS SCORE MILD/MODERATE/SEVERE

8. MRS AFTER ONE MONTH

INVESTIGATIONS

BLOOD:

COMPLETE HAEMOGRAM - Hb.

TC

DC

ESR

PLATELETS

BLOOD – Sugar

Urea

Creatinine

Serum electrolytes Sodium

Potassium

Serum Triglycerides

Serum cholesterol

Serum fibrinogen

URINE ROUTINE :

CHEST X RAY

ECG

ECHO

CT BRAIN

NIHSS SCALE

1a. Level of Consciousness:

0 = Alert; keenly responsive.

1 = Not alert, but arousable by minor stimulation to obey, answer, or respond.

2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).

3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.

Score:

1b. LOC Questions:

0 = Answers both questions correctly.

1 = Answers one question correctly.

2 = Answers neither question correctly.

Score:

1c. LOC Commands:

0 = Performs both tasks correctly

1 = Performs one task correctly

2 = Performs neither task correctly

Score:

2. Best Gaze:

0 = Normal

1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present.

2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneouver.

Score:

3. Visual:

0 = No visual loss

1 = Partial hemianopia

2 = Complete hemianopia

3 = Bilateral hemianopia (blind including cortical blindness)

Score:

4. Facial Palsy:

0 = Normal symmetrical movement

1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)

2 = Partial paralysis (total or near total paralysis of lower face)

3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

Score:

5 & 6. Motor Arm and Leg:

0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds.

1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.

2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.

3 = No effort against gravity, limb falls.

4 = No movement

9 = Amputation, joint fusion , explain: ---------

Score: 5a.Left Arm 5b. Right Arm

0 = No drift, leg holds 30 degrees position for full 5 seconds.

1 = Drift, leg falls by the end of the 5-second period but does not hit bed.

2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.

3 = No effort against gravity, leg falls to bed immediately.

4 = No movement

9 = Amputation, joint fusion , explain: ----------

Score: 6a. Left Leg 6b. Right Leg

7. Limb Ataxia:

0 = Absent

1 = Present in one limb

2 = Present in two limbs If present, is ataxia in

Right arm 1 = Yes 2 = No

Left arm 1 = Yes 2 = No

Right leg 1 = Yes 2 = No

Left leg 1 = Yes 2 = No

9 = amputation or joint fusion, explain----------

Score:

8. Sensory:

0 = Normal; no sensory loss.

1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched.

2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.

Score:

9. Best Language:

0 = No aphasia, normal

1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card from patient's response.

2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of

communication. Examiner cannot identify materials provided from patient response.

3 = Mute, global aphasia; no usable speech or auditory comprehension.

Score:

10. Dysarthria:

0 = Normal

1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty.

2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.

9 = Intubated or other physical barrier, explain----------

Score:

11. Extinction and Inattention (formerly Neglect):

0 = No abnormality.

1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.

Score:

TOTAL SCORE(0 to 42): **AT ADMISSION:**

- >25 Very severe neurological impairment
- 15-24 Severe impairment
- 5-14 Moderately severe impairment
- <5 Mild impairment

(Adams, HP, et al. (1999). Neurology: 53: 126-131)

MODIFIED RANKIN'S SCALE

Score

0= No symptoms at all

1 =No significant disability despite symptoms; able to carry out all usual duties and activities

2 =Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 =Moderate disability; requiring some help, but able to walk without assistance

4 =Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 =Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 =Dead

TOTAL (0–6):

AT ONE MONTH FOLLOW UP:

ABBREVATIONS

aPTT - ACTIVATED PARTIAL THROMBOPLASTIN TIME

ATP - ADENOSINE TRIPHOSPHATE

CNS - CENTRAL NERVOUS SYSTEM

COX - CYCLO OXYGENASE

CRP - C- REACTIVE PROTEIN

ELISA- ENZYME LINKED IMMUNOSORBANT ASSAY

ESR - ERYTHROCYTE SEDIMENTATION RATE

FPA - FIBRINOPEPTIDE A

FPB - FIBRINOPEPTIDE B

Gp - GLYCOPROTEIN

i NOS- INDUCIBLE NITRIC OXIDE SYNTHASE

ICAM-1- INTERCELLULAR ADHESION MOLECULE-1

ICP - INTRA CRANIAL PRESSURE

IHD - ISCHEMIC HEART DISEASE

IL-1 - INTERLEUKIN-1

IL-6 - INTERLEUKIN-6

LDL - LOW DENSITY LIPOPROTEIN CHOLESTEROL

LP(a) - LIPOPROTEIN a

MCP-1- MACOPHAGE CHEMOATTRACTANT PROTEIN-1

MMP - MATRIX METALLOPROTEASES

NH-2 - AMINO TERMINAL

PT - PROTHROMBIN TIME

PT-Fg- PROTHROMBIN DERIVED FIBRINOGEN

PUFA- POLY UNSATURATED FATTY ACID

SLE - SYSTEMIC LUPUS ERYTHEMATOSUS

SNAP25- SYNAPTOSOMAL ASSOCIATED PROTEIN 25

t- PA - TISSUE PLASMINOGEN ACTIVATOR

TIA - TRANSIENT ISCHEMIC ATTACK

TNF α- TUMOR NECROSIS FACTOR-α

TT - THROMBIN TIME

VCAM-1- VASCULAR CELL ADHESION MOLECULE-1

VEGF - VASCULAR ENDOTHELIAL GROWTH FACTOR

WHO - WORLD HEALTH ORGANISATION

SI.NO	NAME	AGE	SEX	HYPERT	DIABETE	SMOKIN	ALCOH	BP	BMI	SUGAR	CHOLES	FIBRINOGEN	CT BRAIN	DIAGNOSIS	NIHSS S	MRS SCORE AT T
1	Murugan	55	MALE	NO	NO	YES	YES	126/80	30	140	270	760	infarct	left hemiplegia	26	5
2	Saroja	68	FEMALE	NO	NO	NO	NO	130/70	26	132	188	560	infarct	right hemiplegia	12	2
3	Sridevi	55	FEMALE	NO	NO	NO	NO	132/80	31	124	200	770	infarct	right hemiplegia	26	5
4	Amirthavalli	65	FEMALE	YES	NO	NO	NO	160/90	29	134	295	640	infarct	left hemiplegia	14	3
5	Kuppammal	70	FEMALE	YES	YES	NO	NO	150/100	24	210	195	410	infarct	right hemiplegia	4	1
6	Rajendran	55	MALE	YES	NO	YES	YES	180/110	32	123	180	620	infarct	left hemiplegia	14	3
7	Jeganathan	35	MALE	NO	NO	YES	NO	120/70	31	110	350	560	infarct	left hemiplegia	10	2
8	Thirupathy	40	MALE	YES	NO	YES	NO	160/96	23	112	368	270	infarct	left hemiplegia	2	0
9	Devi	75	FEMALE	NO	YES	NO	NO	110/60	28	220	156	680	infarct	left hemiplegia	14	3
10	Anjalai	65	FEMALE	YES	NO	NO	NO	162/90	35	150	170	780	infarct	left hemiplegia	28	5
11	Sundaram	60	MALE	YES	NO	YES	YES	180/100	32	174	360	700	infarct	right hemiplegia	20	4
12	Sudalai	59	MALE	YES	YES	YES	YES	170/110	24	220	180	440	infarct	left hemiplegia	4	1
13	Kannammal	65	FEMALE	NO	NO	NO	NO	120/76	32	132	240	730	infarct	right hemiplegia	28	5
14	Datchayani	42	FEMALE	NO	YES	NO	NO	112/60	29	223	160	650	infarct	right hemiplegia	12	3
15	Kathirvel	50	MALE	YES	NO	NO	YES	140/80	30	112	310	700	infarct	right hemiplegia	18	4
16	Arokiyamary	55	FEMALE	NO	YES	NO	NO	114/68	29	120	262	740	infarct	left hemiplegia	26	4
17	Ramalakshmi	70	FEMALE	YES	NO	NO	NO	150/90	34	143	150	750	infarct	left hemiplegia	26	4
18	Anthonyraj	68	MALE	NO	YES	YES	YES	120/60	32	238	274	770	infarct	left hemiplegia	26	4
19	Pandiyan	70	MALE	YES	NO	YES	NO	180/110	29	108	175	680	infarct	left hemiplegia	14	3
20	Anthoniamma	46	FEMALE	YES	NO	NO	NO	170/100	30	148	290	740	infarct	right hemiplegia	26	4
21	Prakasam	70	MALE	NO	NO	YES	NO	124/80	31	138	295	700	infarct	left hemiplegia	20	3
22	Manimegalai	48	FEMALE	YES	NO	NO	NO	160/90	30	145	320	710	infarct	right hemiplegia	20	3
23	Manonmani	68	FEMALE	NO	YES	NO	NO	130/70	29	369	180	720	infarct	right hemiplegia	24	3
24	Arokiyaraj	42	MALE	NO	NO	NO	YES	130/70	30	146	300	700	infarct	left hemiplegia	20	3
25	Adaikalam	70	MALE	NO	NO	NO	NO	120/78	28	163	275	740	infarct	right hemiplegia	26	4
26	Palanisamy	35	MALE	NO	NO	YES	YES	110/70	23	179	360	240	infarct	left hemiplegia	2	0
27	Manimaran	40	MALE	NO	NO	YES	NO	118/80	30	157	310	720	infarct	right hemiplegia	22	3
28	Kandasamy	66	MALE	YES	NO	YES	NO	160/100	30	142	280	840	infarct	right hemiplegia	34	6
29	Muthu	75	MALE	YES	NO	YES	YES	160/110	28	127	190	560	infarct	right hemiplegia	10	2
30	Kulandaivel	65	MALE	YES	YES	YES	YES	140/90	26	220	250	550	infarct	left hemiplegia	12	2
31	Manikkam	70	MALE	YES	NO	YES	NO	150/90	27	134	275	850	infarct	left hemiplegia	36	6
32	Irudayaraj	42	MALE	YES	YES	YES	YES	160/80	22	270	160	200	infarct	right hemiplegia	2	0
33	Padmanaban	48	MALE	NO	YES	YES	NO	130/70	24	230	290	280	infarct	left hemiplegia	4	0
34	Rajakumaran	54	MALE	NO	NO	NO	NO	126/84	35	142	320	720	infarct	right hemiplegia	24	5
35	Kuttiyammal	65	FEMALE	YES	NO	NO	NO	160/90	23	130	200	180	infarct	right hemiplegia	2	0
36	Kumaresan	75	MALE	YES	NO	NO	YES	150/80	22	82	150	410	infarct	left hemiplegia	6	1
37	Vinayagam	40	MALE	NO	NO	YES	NO	120/70	34	163	305	780	infarct	left hemiplegia	30	6
38	Kulanthaimar	35	FEMALE	NO	NO	YES	NO	110/80	33	140	260	760	infarct	left hemiplegia	28	5
39	Gunasundari	60	FEMALE	NO	YES	NO	NO	130/80	35	275	190	780	infarct	left hemiplegia	28	5
40	Prakasam	55	MALE	NO	NO	NO	NO	130/80	31	147	295	740	infarct	left hemiplegia	26	4
41	Parimala	58	FEMALE	NO	YES	NO	NO	126/84	24	260	280	480	infarct	right hemiplegia	8	1
42	Marimuthu	59	MALE	YES	NO	YES	NO	160/100	23	130	175	410	infarct	left hemiplegia	6	1
43	Manikandan	61	MALE	NO	NO	NO	YES	120/70	32	136	320	700	infarct	left hemiplegia	18	3
44	Parameswari	65	FEMALE	YES	YES	NO	NO	150/110	23	280	360	430	infarct	right hemiplegia	4	0
45	Susaiammal	75	FEMALE	NO	YES	NO	NO	130/80	34	267	340	800	infarct	left hemiplegia	30	5
46	Gandhi	70	MALE	NO	NO	YES	YES	120/80	31	143	325	730	infarct	right hemiplegia	24	4
47	Jawahar	55	MALE	NO	YES	NO	NO	110/70	24	220	195	210	infarct	right hemiplegia	2	0
48	Mukesh	45	MALE	NO	NO	YES	NO	120/78	32	162	320	780	infarct	right hemiplegia	28	5
49	ravichandran	47	MALE	YES	NO	YES	NO	150/90	25	153	190	480	infarct	left hemiplegia	6	1
50	Gurusamy	60	MALE	NO	NO	NO	NO	130/80	24	110	185	460	infarct	left hemiplegia	4	1

SI.NO	NAME	AGE	SEX	HYPERTE	DIABETES	SMOKING	ALCOHOI	BP	BMI	SUGAR	CHOLES	FIBRINOGEN
1	Ganesan	55	MALE	NO	NO	YES	YES	120/70	27	130	160	240
2	Dhanalakshmi	68	FEMALE	NO	NO	NO	NO	110/60	24	137	190	130
3	Madhavi	55	FEMALE	NO	NO	NO	NO	130/80	25	110	180	250
4	Saradha	65	FEMALE	YES	NO	NO	NO	150/90	30	167	280	200
5	Mekala	75	FEMALE	YES	YES	NO	NO	160/100	29	254	250	190
6	Harikrishnan	55	MALE	YES	NO	YES	YES	150/90	27	98	240	170
7	Senthil	35	MALE	NO	NO	YES	NO	124/80	30	120	290	240
8	Jayaraman	40	MALE	YES	NO	YES	NO	144/90	34	134	300	170
9	Jagadeeswari	70	FEMALE	NO	YES	NO	NO	120/80	21	240	160	160
10	Vadivu	65	FEMALE	YES	NO	NO	NO	150/90	24	160	180	320
11	mannan	60	MALE	YES	NO	YES	YES	160/90	37	170	320	560
12	Arumugam	59	MALE	YES	YES	YES	YES	170/100	24	230	200	490
13	Annalakshmi	65	FEMALE	NO	NO	NO	NO	110/70	23	120	160	170
14	Banumathi	42	FEMALE	NO	YES	NO	NO	110/60	26	245	170	320
15	Chinnathambi	50	MALE	YES	NO	NO	YES	150/100	30	121	300	250
16	Daulath	55	FEMALE	NO	YES	NO	NO	120/80	25	290	180	190
17	Gnanamary	70	FEMALE	YES	NO	NO	NO	160/100	23	133	160	190
18	Elanchezhian	68	MALE	NO	YES	YES	YES	110/70	27	287	260	280
19	Fakrudeen	70	MALE	YES	NO	YES	NO	160/100	29	90	280	240
20	Hemavathi	46	FEMALE	YES	NO	NO	NO	150/90	29	126	290	220
21	Inbarajan	70	MALE	NO	NO	YES	NO	110/70	32	146	270	360
22	Janaki	48	FEMALE	YES	NO	NO	NO	160/100	30	163	170	160
23	Kaaleeswari	68	FEMALE	NO	YES	NO	NO	110/80	29	274	250	220
24	Loganathan	42	MALE	NO	NO	NO	YES	120/80	30	137	160	400
25	Musthafa	70	MALE	NO	NO	NO	NO	100/70	28	148	250	450
26	Narayanasamy	35	MALE	NO	NO	YES	YES	110/70	34	148	310	190
27	Puthiyavan	40	MALE	NO	NO	YES	NO	120/80	30	132	180	250
28	Rajeshwaran	66	MALE	YES	NO	YES	NO	150/90	30	153	270	540
29	Sundaralingam	75	MALE	YES	NO	YES	YES	160/100	28	120	250	240
30	Thiyagarajan	65	MALE	YES	YES	YES	NO	150/100	31	301	290	550
31	Udhayan	70	MALE	YES	NO	YES	NO	160/90	26	116	175	680
32	Velusamy	42	MALE	YES	YES	YES	YES	150/90	30	310	300	280
33	Yesuraj	48	MALE	NO	YES	YES	NO	110/70	32	320	320	200
34	Aadhibagavan	54	MALE	NO	NO	NO	NO	100/60	25	128	200	440
35	Durgambal	65	FEMALE	YES	NO	NO	NO	160/100	28	120	270	360
36	Boopathi	75	MALE	YES	NO	NO	YES	170/90	34	117	320	380
37	Chandran	40	MALE	NO	NO	YES	NO	110/70	30	95	300	380
38	Elumalai	35	MALE	NO	NO	YES	NO	120/70	37	108	195	190
39	Gandhimathi	60	FEMALE	NO	YES	NO	NO	120/80	28	253	150	170
40	Harichandran	55	MALE	NO	NO	NO	NO	100/60	31	136	180	270
41	Indrani	58	FEMALE	NO	YES	NO	NO	110/70	28	210	270	190
42	Jayamurugan	59	MALE	YES	NO	YES	NO	150/100	30	138	300	400
43	Karikalan	60	MALE	NO	NO	NO	YES	110/70	29	163	290	540
44	Loganayaki	65	FEMALE	YES	YES	NO	NO	160/100	32	290	310	160
45	Muthumari	75	FEMALE	NO	YES	NO	NO	100/70	29	307	290	190
46	Nedunchelian	70	MALE	NO	NO	YES	YES	100/60	32	130	260	400
47	Parasuraman	55	MALE	NO	YES	NO	NO	110/70	30	274	195	500
48	Ragavendran	45	MALE	NO	NO	YES	NO	120/80	32	148	320	400
49	Sabari	44	MALE	YES	NO	YES	NO	160/100	31	110	310	190
50	Thilakamma	60	FEMALE	NO	NO	NO	YES	100/70	34	100	190	180

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.1223/ME-1/Ethics/2013 Dt:07.03.2013.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on serum level of fibrinogen and its prognostic significance in patients with acute ischemic stroke" for Project work submitted by Dr.A.T.Appuraj, MD (General Medicine) II nd year PG Student, Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

19/4/13

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

GOVT. KILPAUK MEDICAL COLLEGE
19 APR 2013
Kilpauk, Chennai-10.